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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/12, 5/10, G01N 33/50, C07K 16/28, C12Q 1/68, C07K 14/705		A1	(11) International Publication Number: WO 95/04822
			(43) International Publication Date: 16 February 1995 (16.02.95)
(21) International Application Number: PCT/US94/09230		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 11 August 1994 (11.08.94)			
(30) Priority Data: 08/105,536 11 August 1993 (11.08.93) US 08/149,097 5 November 1993 (05.11.93) US			
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(54) Title: HUMAN CALCIUM CHANNEL COMPOSITIONS AND METHODS USING THEM

(57) Abstract

Isolated DNA encoding each of human calcium channel α_1 -, α_2 -, β - and γ -subunits, including subunits that arise as splice variants of primary transcripts, is provided. In particular DNA clones encoding each of the α_{1A-1} , α_{1A-2} , α_{1E-1} , α_{1C-2} , α_{1E-3} , β_3-1 , β_{2C} , β_{2D} , β_{2E} and β_4 subunits of human calcium channels are provided. Cells and vectors containing the DNA, subunit specific antibodies and nucleic acid probes and methods for identifying compounds that modulate the activity of human calcium channels are also provided.

PD-5947-01-DRK

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HUMAN CALCIUM CHANNEL COMPOSITIONS AND METHODS USING THEM

TECHNICAL FIELD

The present invention relates to molecular biology and pharmacology. More particularly, the invention relates to calcium channel compositions and methods of making and using the same.

BACKGROUND OF THE INVENTION

Calcium channels are membrane-spanning, multi-subunit proteins that allow controlled entry of Ca^{2+} ions into cells from the extracellular fluid. Cells throughout the animal kingdom, and at least some bacterial, fungal and plant cells, possess one or more types of calcium channel.

The most common type of calcium channel is voltage dependent. "Opening" of a voltage-dependent channel to allow an influx of Ca^{2+} ions into the cells requires a depolarization to a certain level of the potential difference between the inside of the cell bearing the channel and the extracellular medium bathing the cell. The rate of influx of Ca^{2+} into the cell depends on this potential difference. All "excitable" cells in animals, such as neurons of the central nervous system (CNS), peripheral nerve cells and muscle cells, including those of skeletal muscles, cardiac muscles, and venous and arterial smooth muscles, have voltage-dependent calcium channels.

Multiple types of calcium channels have been identified in mammalian cells from various tissues, including skeletal muscle, cardiac muscle, lung, smooth muscle and brain, [see, e.g., Bean, B.P. (1989) *Ann. Rev. Physiol.* 51:367-384 and Hess, P. (1990) *Ann. Rev. Neurosci.* 56:337]. The different types of calcium channels have been broadly categorized into four classes, L-, T-, N-, and P-type, distinguished by current kinetics, holding potential sensitivity and sensitivity to calcium channel agonists and antagonists.

Calcium channels are multisubunit proteins that contain two large subunits, designated α_1 and α_2 , which have molecular weights between about 130 and about 200 kilodaltons ("kD"),

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and one to three different smaller subunits of less than about 60 kD in molecular weight. At least one of the larger subunits and possibly some of the smaller subunits are glycosylated. Some of the subunits are capable of being phosphorylated. The α_1 subunit has a molecular weight of about 150 to about 170 kD when analyzed by sodium dodecylsulfate (SDS)-polyacrylamide gel electrophoresis (PAGE) after isolation from mammalian muscle tissue and has specific binding sites for various 1,4-dihydropyridines (DHPs) and phenylalkylamines. Under non-reducing conditions (in the presence of N-ethylmaleimide), the α_2 subunit migrates in SDS-PAGE as a band corresponding to a molecular weight of about 160-190 kD. Upon reduction, a large fragment and smaller fragments are released. The β subunit of the rabbit skeletal muscle calcium channel is a phosphorylated protein that has a molecular weight of 52-65 kD as determined by SDS-PAGE analysis. This subunit is insensitive to reducing conditions. The γ subunit of the calcium channel, which is not observed in all purified preparations, appears to be a glycoprotein with an apparent molecular weight of 30-33 kD, as determined by SDS-PAGE analysis.

In order to study calcium channel structure and function, large amounts of pure channel protein are needed. Because of the complex nature of these multisubunit proteins, the varying concentrations of calcium channels in tissue sources of the protein, the presence of mixed populations of calcium channels in tissues, difficulties in obtaining tissues of interest, and the modifications of the native protein that can occur during the isolation procedure, it is extremely difficult to obtain large amounts of highly purified, completely intact calcium channel protein.

Characterization of a particular type of calcium channel by analysis of whole cells is severely restricted by the presence of mixed populations of different types of calcium channels in the majority of cells. Single-channel recording methods that are used to examine individual calcium channels

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do not reveal any information regarding the molecular structure or biochemical composition of the channel. Furthermore, in performing this type of analysis, the channel is isolated from other cellular constituents that might be important for natural functions and pharmacological interactions.

Characterization of the gene or genes encoding calcium channels provides another means of characterization of different types of calcium channels. The amino acid sequence determined from a complete nucleotide sequence of the coding region of a gene encoding a calcium channel protein represents the primary structure of the protein. Furthermore, secondary structure of the calcium channel protein and the relationship of the protein to the membrane may be predicted based on analysis of the primary structure. For instance, hydropathy plots of the α_1 subunit protein of the rabbit skeletal muscle calcium channel indicate that it contains four internal repeats, each containing six putative transmembrane regions [Tanabe, T. et al. (1987) *Nature* 328:313].

Because calcium channels are present in various tissues and have a central role in regulating intracellular calcium ion concentrations, they are implicated in a number of vital processes in animals, including neurotransmitter release, muscle contraction, pacemaker activity, and secretion of hormones and other substances. These processes appear to be involved in numerous human disorders, such as CNS and cardiovascular diseases. Calcium channels, thus, are also implicated in numerous disorders. A number of compounds useful for treating various cardiovascular diseases in animals, including humans, are thought to exert their beneficial effects by modulating functions of voltage-dependent calcium channels present in cardiac and/or vascular smooth muscle. Many of these compounds bind to calcium channels and block, or reduce the rate of, influx of Ca^{2+} into the cells in response to depolarization of the cell membrane.

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The results of studies of recombinant expression of rabbit calcium channel α_1 subunit-encoding cDNA clones and transcripts of the cDNA clones indicate that the α_1 subunit forms the pore through which calcium enters cells. The relevance of the barium currents generated in these recombinant cells to the actual current generated by calcium channels containing as one component the respective α_1 subunits *in vivo* is unclear. In order to completely and accurately characterize and evaluate different calcium channel types, however, it is essential to examine the functional properties of recombinant channels containing all of the subunits as found *in vivo*.

In order to conduct this examination and to fully understand calcium channel structure and function, it is critical to identify and characterize as many calcium channel subunits as possible. Also in order to prepare recombinant cells for use in identifying compounds that interact with calcium channels, it is necessary to be able to produce cells that express uniform populations of calcium channels containing defined subunits.

An understanding of the pharmacology of compounds that interact with calcium channels in other organ systems, such as the CNS, may aid in the rational design of compounds that specifically interact with subtypes of human calcium channels to have desired therapeutic effects, such as in the treatment of neurodegenerative and cardiovascular disorders. Such understanding and the ability to rationally design therapeutically effective compounds, however, have been hampered by an inability to independently determine the types of human calcium channels and the molecular nature of individual subtypes, particularly in the CNS, and by the unavailability of pure preparations of specific channel subtypes to use for evaluation of the specificity of calcium channel-affecting compounds. Thus, identification of DNA encoding human calcium channel subunits and the use of such DNA for expression of calcium channel subunits and functional

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calcium channels would aid in screening and designing therapeutically effective compounds.

Therefore, it is an object herein, to provide DNA encoding specific calcium channel subunits and to provide eukaryotic cells bearing recombinant tissue-specific or subtype-specific calcium channels. It is also an object to provide assays for identification of potentially therapeutic compounds that act as calcium channel antagonists and agonists.

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SUMMARY OF THE INVENTION

Isolated and purified nucleic acid fragments that encode human calcium channel subunits are provided. DNA encoding α_1 subunits of a human calcium channel, and RNA, encoding such subunits, made upon transcription of such DNA are provided. In particular, DNA fragments encoding α_1 subunits of voltage-dependent human calcium channels (VDCCs) type A, type B (also referred to as VDCC IV), type C (also referred to as VDCC II) type D (also referred to as VDCC III) and type E are provided.

DNA encoding α_{1A} , α_{1B} , α_{1C} , α_{1D} and α_{1E} subunits is provided.

DNA encoding an α_{1D} subunit that includes the amino acids substantially as set forth as residues 10-2161 of SEQ ID No. 1 is provided. DNA encoding an α_{1D} subunit that includes substantially the amino acids set forth as amino acids 1-34 in SEQ ID No. 2 in place of amino acids 373-406 of SEQ ID No. 1 is also provided. DNA encoding an α_{1C} subunit that includes the amino acids substantially as set forth in SEQ ID No. 3 or SEQ ID No. 6 and DNA encoding an α_{1B} subunit that includes an amino acid sequence substantially as set forth in SEQ ID No. 7 or in SEQ ID No. 8 is also provided.

DNA encoding α_{1A} subunits is also provided. Such DNA includes DNA encoding an α_{1A} subunit that has substantially the same sequence of amino acids as encoded by the DNA set forth in SEQ ID No. 22 or No. 23 or other splice variants of α_{1A} that include all or part of the sequence set forth in SEQ ID No. 22 or 23. The sequence set forth in SEQ ID NO. 22 is a splice variant designated α_{1A-1} ; and the sequence set forth in SEQ ID NO. 23 is a splice variant designated α_{1A-2} . DNA encoding α_{1A} subunits also include DNA encoding subunits that can be isolated using all or a portion of the DNA having SEQ ID NO. 21, 22 or 23 or DNA obtained from the phage lysate of an *E. coli* host containing DNA encoding an α_{1A} subunit that has been deposited in the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852 U.S.A. under Accession No. 75293 in accord with the Budapest Treaty. The

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DNA in such phage includes a DNA fragment having the sequence set forth in SEQ ID No. 21. This fragment selectively hybridizes under conditions of high stringency to DNA encoding α_{1A} but not to DNA encoding α_{1B} and, thus, can be used to isolate DNA that encodes α_{1A} subunits.

DNA encoding α_{1E} subunits of a human calcium channel is also provided. This DNA includes DNA that encodes an α_{1E} splice variant designated α_{1E-1} encoded by the DNA set forth in SEQ ID No. 24, and a variant designated α_{1E-3} encoded by SEQ ID No. 25. This DNA also includes other splice variants thereof that encodes sequences of amino acids encoded by all or a portion of the sequences of nucleotides set forth in SEQ ID Nos. 24 and 25 and DNA that hybridizes under conditions of high stringency to the DNA of SEQ ID No. 24 or 25 and that encodes an α_{1E} splice variant.

DNA encoding α_2 subunits of a human calcium channel, and RNA encoding such subunits, made upon transcription of such a DNA are provided. DNA encoding splice variants of the α_2 subunit, including tissue-specific splice variants, are also provided. In particular, DNA encoding the α_{2a} - α_{2e} subunit subtypes is provided. In particularly preferred embodiments, the DNA encoding the α_2 subunit that is produced by alternative processing of a primary transcript that includes DNA encoding the amino acids set forth in SEQ ID 11 and the DNA of SEQ ID No. 13 inserted between nucleotides 1624 and 1625 of SEQ ID No. 11 is provided. The DNA and amino acid sequences of α_{2a} - α_{2e} are set forth in SEQ. ID Nos. 11 and 29-32, respectively.

Isolated and purified DNA fragments encoding human calcium channel β subunits, including DNA encoding β_1 , β_2 , β_3 and β_4 subunits, and splice variants of the β subunits are provided. RNA encoding β subunits, made upon transcription of the DNA is also provided.

DNA encoding a β_1 subunit that is produced by alternative processing of a primary transcript that includes DNA encoding the amino acids set forth in SEQ ID No. 9, but including the

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DNA set forth in SEQ ID No. 12 inserted in place of nucleotides 615-781 of SEQ ID No. 9 is also provided. DNA encoding β_1 subunits that are encoded by transcripts that have the sequence set forth in SEQ ID No. 9 including the DNA set forth in SEQ ID No. 12 inserted in place of nucleotides 615-781 of SEQ ID No. 9, but that lack one or more of the following sequences of nucleotides: nucleotides 14-34 of SEQ ID No. 12, nucleotides 13-34 of SEQ ID No. 12, nucleotides 35-55 of SEQ ID No. 12, nucleotides 56-190 of SEQ ID No. 12 and nucleotides 191-271 of SEQ ID No. 12 are also provided. In particular, β_1 subunit splice variants $\beta_{1.1}$ - $\beta_{1.5}$ (see, SEQ ID Nos. 9, 10 and 33-35) described below, are provided.

β_2 subunit splice variants β_{2c} - β_{2e} , that include all or a portion of SEQ ID Nos. 26, 29 and 30 are provided; β_3 subunit splice variants, including β_3 subunit splice variants that have the sequences set forth in SEQ ID Nos 19 and 20, and DNA encoding the β_4 subunit that includes DNA having the sequence set forth in SEQ ID No. 27 and the amino acid sequence set forth in SEQ ID No. 28 are provided.

Also *Escherichia coli* (*E. coli*) host cells harboring plasmids containing DNA encoding β_3 have been deposited in accord with the Budapest Treaty under Accession No. 69048 at the American Type Culture Collection. The deposited clone encompasses nucleotides 122-457 in SEQ ID No. 19 and 107-443 in SEQ ID No. 20.

DNA encoding β subunits that are produced by alternative processing of a primary transcript encoding a β subunit, including a transcript that includes DNA encoding the amino acids set forth in SEQ ID No. 9 or including a primary transcript that encodes β_3 as deposited under ATCC Accession No. 69048, but lacking and including alternative exons are provided or may be constructed from the DNA provided herein.

DNA encoding γ subunits of human calcium channels is also provided. RNA, encoding γ subunits, made upon transcription of the DNA are also provided. In particular, DNA containing

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the sequence of nucleotides set forth in SEQ ID No. 14 is provided.

Full-length DNA clones and corresponding RNA transcripts, encoding α_1 , including splice variants of α_{1A} , α_{1D} , α_{1B} , α_{1C} , and α_{1E} , α_2 and β subunits, including β_{1-1} - β_{1-5} , β_{2C} , β_{2D} , β_{2E} , β_{3-1} and β_4 of human calcium channels are provided. Also provided are DNA clones encoding a substantial portions of the certain α_{1C} subtype subunits and γ subunits of voltage-dependent human calcium channels for the preparation of full-length DNA clones encoding the corresponding full-length subunits. Full-length clones may be readily obtained using the disclosed DNA as a probe as described herein.

The the α_{1A} subunit, α_{1C} subunit, α_{1E} subunit and splice variants thereof, the β_{2D} , β_{2C} and β_{2E} subunits and β_4 subunits and nucleic acids encoding these subunits are of particular interest herein.

Eukaryotic cells containing heterologous DNA encoding one or more calcium channel subunits, particularly human calcium channel subunits, or containing RNA transcripts of DNA clones encoding one or more of the subunits are provided. A single α_1 subunit can form a channel. The requisite combination of subunits for formation of active channels in selected cells, however, can be determined empirically using the methods herein. For example, if a selected α_1 subtype or variant does not form an active channel in a selected cell line, an additional subunit or subunits can be added until an active channel is formed.

In preferred embodiments, the cells contain DNA or RNA encoding a human α_1 subunit, preferably at least an α_{1D} , α_{1B} , α_{1A} or α_{1E} subunit. In more preferred embodiments, the cells contain DNA or RNA encoding additional heterologous subunits, including at least one β , α_2 or γ subunit. In such embodiments, eukaryotic cells stably or transiently transfected with any combination of one, two, three or four of the subunit-encoding DNA clones, such as DNA encoding any of α_1 , $\alpha_1 + \beta$, $\alpha_1 + \beta + \alpha_2$, are provided.

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The eukaryotic cells provided herein contain heterologous DNA that encodes an α_1 subunit or heterologous DNA that encodes an α_1 subunit and heterologous DNA that encodes a β subunit. At least one subunit is selected α_{1A-1} , α_{1A-2} , α_{1C-2} , α_{1E-1} , α_{1E-3} , β_{2C} , β_{2D} , β_{2F} , a β_{3-1} , β_{3-2} subunit or a β_4 subunit. In preferred embodiments, the cells express such heterologous calcium channel subunits and include one or more of the subunits in membrane-spanning heterologous calcium channels. In more preferred embodiments, the eukaryotic cells express functional, heterologous calcium channels that are capable of gating the passage of calcium channel-selective ions and/or binding compounds that, at physiological concentrations, modulate the activity of the heterologous calcium channel. In certain embodiments, the heterologous calcium channels include at least one heterologous calcium channel subunit. In most preferred embodiments, the calcium channels that are expressed on the surface of the eukaryotic cells are composed substantially or entirely of subunits encoded by the heterologous DNA or RNA. In preferred embodiments, the heterologous calcium channels of such cells are distinguishable from any endogenous calcium channels of the host cell. Such cells provide a means to obtain homogeneous populations of calcium channels. Typically, the cells contain the selected calcium channel as the only heterologous ion channel expressed by the cell.

In certain embodiments the recombinant eukaryotic cells that contain the heterologous DNA encoding the calcium channel subunits are produced by transfection with DNA encoding one or more of the subunits or are injected with RNA transcripts of DNA encoding one or more of the calcium channel subunits. The DNA may be introduced as a linear DNA fragment or may be included in an expression vector for stable or transient expression of the subunit-encoding DNA. Vectors containing DNA encoding human calcium channel subunits are also provided.

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The eukaryotic cells that express heterologous calcium channels may be used in assays for calcium channel function or, in the case of cells transformed with fewer subunit-encoding nucleic acids than necessary to constitute a functional recombinant human calcium channel, such cells may be used to assess the effects of additional subunits on calcium channel activity. The additional subunits can be provided by subsequently transfecting such a cell with one or more DNA clones or RNA transcripts encoding human calcium channel subunits.

The recombinant eukaryotic cells that express membrane spanning heterologous calcium channels may be used in methods for identifying compounds that modulate calcium channel activity. In particular, the cells are used in assays that identify agonists and antagonists of calcium channel activity in humans and/or assessing the contribution of the various calcium channel subunits to the transport and regulation of transport of calcium ions. Because the cells constitute homogeneous populations of calcium channels, they provide a means to identify agonists or antagonists of calcium channel activity that are specific for each such population.

The assays that use the eukaryotic cells for identifying compounds that modulate calcium channel activity are also provided. In practicing these assays the eukaryotic cell that expresses a heterologous calcium channel, containing at least one subunit encoded by the DNA provided herein, is in a solution containing a test compound and a calcium channel selective ion, the cell membrane is depolarized, and current flowing into the cell is detected. If the test compound is one that modulates calcium channel activity, the current that is detected is different from that produced by depolarizing the same or a substantially identical cell in the presence of the same calcium channel-selective ion but in the absence of the compound. In preferred embodiments, prior to the depolarization step, the cell is maintained at a holding potential which substantially inactivates calcium channels

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which are endogenous to the cell. Also in preferred embodiments, the cells are mammalian cells, most preferably HEK cells, or amphibian oocytes.

Nucleic acid probes, typically labeled for detection, containing at least about 14, preferably 16, or, if desired, 20 or 30 or more, contiguous nucleotides of α_{1D} , α_{1C} , α_{1B} , α_{1A} and α_{1E} , α_2 , β , including β_1 , β_2 , β_3 and β_4 splice variants and γ subunit-encoding DNA are provided. Methods using the probes for the isolation and cloning of calcium channel subunit-encoding DNA, including splice variants within tissues and inter-tissue variants are also provided.

Purified human calcium channel subunits and purified human calcium channels are provided. The subunits and channels can be isolated from a eukaryotic cell transfected with DNA that encodes the subunit.

In another embodiment, immunoglobulins or antibodies obtained from the serum of an animal immunized with a substantially pure preparation of a human calcium channel, human calcium channel subunit or epitope-containing fragment of a human calcium subunit are provided. Monoclonal antibodies produced using a human calcium channel, human calcium channel subunit or epitope-containing fragment thereof as an immunogen are also provided. *E. coli* fusion proteins including a fragment of a human calcium channel subunit may also be used as immunogen. Such fusion proteins may contain a bacterial protein or portion thereof, such as the *E. coli* TrpE protein, fused to a calcium channel subunit peptide. The immunoglobulins that are produced using the calcium channel subunits or purified calcium channels as immunogens have, among other properties, the ability to specifically and preferentially bind to and/or cause the immunoprecipitation of a human calcium channel or a subunit thereof which may be present in a biological sample or a solution derived from such a biological sample. Such antibodies may also be used to selectively isolate cells that express calcium channels that contain the subunit for which the antibodies are specific.

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Methods for modulating the activity of ion channels by contacting the calcium channels with an effective amount of the above-described antibodies are also provided.

A diagnostic method for determining the presence of Lambert Eaton Syndrome (LES) in a human based on immunological reactivity of LES immunoglobulin G (IgG) with a human calcium channel subunit or a eukaryotic cell which expresses a recombinant human calcium channel or a subunit thereof is also provided. In particular, an immunoassay method for diagnosing Lambert-Eaton Syndrome in a person by combining serum or an IgG fraction from the person (test serum) with calcium channel proteins, including the α and β subunits, and ascertaining whether antibodies in the test serum react with one or more of the subunits, or a recombinant cell which expresses one or more of the subunits to a greater extent than antibodies in control serum, obtained from a person or group of persons known to be free of the Syndrome, is provided. Any immunoassay procedure known in the art for detecting antibodies against a given antigen in serum can be employed in the method.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference herein.

Reference to each of the calcium channel subunits includes the subunits that are specifically disclosed herein and human calcium channel subunits encoded by DNA that can be isolated by using the DNA disclosed as probes and screening an appropriate human cDNA or genomic library under at least low stringency. Such DNA also includes DNA that encodes proteins that have about 40% homology to any of the subunits proteins described herein or DNA that hybridizes under conditions of at least low stringency to the DNA provided herein and the

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protein encoded by such DNA exhibits additional identifying characteristics, such as function or molecular weight.

It is understood that subunits that are encoded by transcripts that represent splice variants of the disclosed subunits or other such subunits may exhibit less than 40% overall homology to any single subunit, but will include regions of such homology to one or more such subunits. It is also understood that 40% homology refers to proteins that share approximately 40% of their amino acids in common or that share somewhat less, but include conservative amino acid substitutions, whereby the activity of the protein is not substantially altered.

As used herein, the α_1 subunits types, encoded by different genes, are designated as type α_{1A} , α_{1B} , α_{1C} , α_{1D} and α_{1E} . These types have also been referred to as VDCC IV for α_{1B} , VDCC II for α_{1C} and VDCC III for α_{1D} . Subunit subtypes, which are splice variants, are referred to, for example as α_{1B-1} , α_{1B-2} , α_{1C-1} etc.

Thus, as used herein, DNA encoding the α_1 subunit refers to DNA that hybridizes to the DNA provided herein under conditions of at least low stringency or encodes a subunit that has at least about 40% homology to protein encoded by DNA disclosed herein that encodes an α_1 subunit of a human calcium. An α_1 subunit may be identified by its ability to form a calcium channel. Typically, α_1 subunits have molecular masses greater than at least about 120 kD. Also, hydropathy plots of deduced α_1 subunit amino acid sequences indicate that the α_1 subunits contain four internal repeats, each containing six putative transmembrane domains.

The activity of a calcium channel may be assessed in vitro by methods known to those of skill in the art, including the electrophysiological and other methods described herein. Typically, α_1 subunits include regions to which one or more modulators of calcium channel activity, such as a 1,4-DHP or ω -CgTx, interact directly or indirectly. Types of α_1 subunits may be distinguished by any method known to those of skill in

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the art, including on the basis of binding specificity. For example, it has been found herein that α_{1B} subunits participate in the formation channels that have previously been referred to as N-type channels, α_{1D} subunits participate in the formation of channels that had previously been referred to as L-type channels, and α_{1A} subunits appear to participate in the formation of channels that exhibit characteristics typical of channels that had previously been designated P-type channels. Thus, for example, the activity of channels that contain the α_{1B} subunit are insensitive to 1,4-DHPs; whereas the activity of channels that contain the α_{1D} subunit are modulated or altered by a 1,4-DHP. It is presently preferable to refer to calcium channels based on pharmacological characteristics and current kinetics and to avoid historical designations. Types and subtypes of α_1 subunits may be characterized on the basis of the effects of such modulators on the subunit or a channel containing the subunit as well as differences in currents and current kinetics produced by calcium channels containing the subunit.

As used herein, an α_2 subunit is encoded by DNA that hybridizes to the DNA provided herein under conditions of low stringency or encodes a protein that has at least about 40% homology with that disclosed herein. Such DNA encodes a protein that typically has a molecular mass greater than about 120 kD, but does not form a calcium channel in the absence of an α_1 subunit, and may alter the activity of a calcium channel that contains an α_1 subunit. Subtypes of the α_2 subunit that arise as splice variants are designated by lower case letter, such as α_{2a} , . . . α_{2e} . In addition, the α_2 subunit and the large fragment produced when the protein is subjected to reducing conditions appear to be glycosylated with at least N-linked sugars and do not specifically bind to the 1,4-DHPs and phenylalkylamines that specifically bind to the α_1 subunit. The smaller fragment, the C-terminal fragment, is referred to as the δ subunit and includes amino acids from about 946 (SEQ ID No. 11) through about the C-terminus. This

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fragment may dissociate from the remaining portion of α_2 when the α_2 subunit is exposed to reducing conditions.

As used herein, a β subunit is encoded by DNA that hybridizes to the DNA provided herein under conditions of low stringency or encodes a protein that has at least about 40% homology with that disclosed herein and is a protein that typically has a molecular mass lower than the α subunits and on the order of about 50-80 kD, does not form a detectable calcium channel in the absence of an α_1 subunit, but may alter the activity of a calcium channel that contains an α_1 subunit or that contains an α_1 and α_2 subunit.

Types of the β subunit that are encoded by different genes are designated with subscripts, such as β_1 , β_2 , β_3 , and β_4 . Subtypes of β subunits that arise as splice variants of a particular type are designated with a numerical subscript referring to the type and to the variant. Such subtypes include, but are not limited to the β_1 splice variants, including $\beta_{1.1}$ - $\beta_{1.5}$, and β_2 variants, including β_{2c} - β_{2e} .

As used herein, a γ subunit is a subunit encoded by DNA disclosed herein as encoding the γ subunit and may be isolated and identified using the DNA disclosed herein as a probe by hybridization or other such method known to those of skill in the art, whereby full-length clones encoding a γ subunit may be isolated or constructed. A γ subunit will be encoded by DNA that hybridizes to the DNA provided herein under conditions of low stringency or exhibits sufficient sequence homology to encode a protein that has at least about 40% homology with the γ subunit described herein.

Thus, one of skill in the art, in light of the disclosure herein, can identify DNA encoding α_1 , α_2 , β , δ and γ calcium channel subunits, including types encoded by different genes and subtypes that represent splice variants. For example, DNA probes based on the DNA disclosed herein may be used to screen an appropriate library, including a genomic or cDNA library, for hybridization to the probe and obtain DNA in one or more clones that includes an open reading fragment that

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encodes an entire protein. Subsequent to screening an appropriate library with the DNA disclosed herein, the isolated DNA can be examined for the presence of an open reading frame from which the sequence of the encoded protein may be deduced. Determination of the molecular weight and comparison with the sequences herein should reveal the identity of the subunit as an α_1 , α_2 , etc. subunit. Functional assays may, if necessary, be used to determine whether the subunit is an α_1 , α_2 subunit or β subunit.

For example, DNA encoding an α_{1A} subunit may be isolated by screening an appropriate library with DNA, encoding all or a portion of the human α_{1A} subunit. Such DNA includes the DNA in the phage deposited under ATCC Accession No. 75293 that encodes a portion of an α_1 subunit. DNA encoding an α_{1A} subunit may be obtained from an appropriate library by screening with an oligonucleotide having all or a portion of the sequence set forth in SEQ ID No. 21, 22 and/or 23 or with the DNA in the deposited phage. Alternatively, such DNA may have a sequence that encodes an α_{1A} subunit that is encoded by SEQ ID NO. 22 or 23.

Similarly, DNA encoding β , may be isolated by screening a human cDNA library with DNA probes prepared from the plasmid $\beta 1.42$ deposited under ATCC Accession No. 69048 or obtained from an appropriate library using probes having sequences prepared according to the sequences set forth in SEQ ID Nos. 19 and/or 20. Also, DNA encoding β , may be isolated by screening a human cDNA library with DNA probes prepared according to DNA set forth in SEQ ID No. 27, which sets forth the DNA sequence of a clone encoding a β , subunit. The amino acid sequence is set forth in SEQ ID No. 28. Any method known to those of skill in the art for isolation and identification of DNA and preparation of full-length genomic or cDNA clones, including methods exemplified herein, may be used. DNA encoding

The subunit encoded by isolated DNA may be identified by comparison with the DNA and amino acid sequences of the

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subunits provided herein. Splice variants share extensive regions of homology, but include non-homologous regions, subunits encoded by different genes share a uniform distribution of non-homologous sequences.

As used herein, a splice variant refers to a variant produced by differential processing of a primary transcript of genomic DNA that results in more than one type of mRNA. Splice variants may occur within a single tissue type or among tissues (tissue-specific variants). Thus, cDNA clones that encode calcium channel subunit subtypes that have regions of identical amino acids and regions of different amino acid sequences are referred to herein as "splice variants".

As used herein, a "calcium channel-selective ion" is an ion that is capable of flowing through, or being blocked from flowing through, a calcium channel which spans a cellular membrane under conditions which would substantially similarly permit or block the flow of Ca^{2+} . Ba^{2+} is an example of an ion which is a calcium channel-selective ion.

As used herein, a compound that modulates calcium channel activity is one that affects the ability of the calcium channel to pass calcium channel-selective ions or affects other detectable calcium channel features, such as current kinetics. Such compounds include calcium channel antagonists and agonists and compounds that exert their effect on the activity of the calcium channel directly or indirectly.

As used herein, a "substantially pure" subunit or protein is a subunit or protein that is sufficiently free of other polypeptide contaminants to appear homogeneous by SDS-PAGE or to be unambiguously sequenced.

As used herein, selectively hybridize means that a DNA fragment hybridizes to a second fragment with sufficient specificity to permit the second fragment to be identified or isolated from among a plurality of fragments. In general, selective hybridization occurs at conditions of high stringency.

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As used herein, heterologous or foreign DNA and RNA are used interchangeably and refer to DNA or RNA that does not occur naturally as part of the genome in which it is present or which is found in a location or locations in the genome that differ from that in which it occurs in nature. It is DNA or RNA that is not endogenous to the cell and has been artificially introduced into the cell. Examples of heterologous DNA include, but are not limited to, DNA that encodes a calcium channel subunit and DNA that encodes RNA or proteins that mediate or alter expression of endogenous DNA by affecting transcription, translation, or other regulatable biochemical processes. The cell that expresses the heterologous DNA, such as DNA encoding a calcium channel subunit, may contain DNA encoding the same or different calcium channel subunits. The heterologous DNA need not be expressed and may be introduced in a manner such that it is integrated into the host cell genome or is maintained episomally.

As used herein, operative linkage of heterologous DNA to regulatory and effector sequences of nucleotides, such as promoters, enhancers, transcriptional and translational stop sites, and other signal sequences, refers to the functional relationship between such DNA and such sequences of nucleotides. For example, operative linkage of heterologous DNA to a promoter refers to the physical and functional relationship between the DNA and the promoter such that the transcription of such DNA is initiated from the promoter by an RNA polymerase that specifically recognizes, binds to and transcribes the DNA in reading frame.

As used herein, isolated, substantially pure DNA refers to DNA fragments purified according to standard techniques employed by those skilled in the art [see, e.g., Maniatis et al. (1982) *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY].

As used herein, expression refers to the process by which nucleic acid is transcribed into mRNA and translated into

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peptides, polypeptides, or proteins. If the nucleic acid is derived from genomic DNA, expression may, if an appropriate eukaryotic host cell or organism is selected, include splicing of the mRNA.

As used herein, vector or plasmid refers to discrete elements that are used to introduce heterologous DNA into cells for either expression of the heterologous DNA or for replication of the cloned heterologous DNA. Selection and use of such vectors and plasmids are well within the level of skill of the art.

As used herein, expression vector includes vectors capable of expressing DNA fragments that are in operative linkage with regulatory sequences, such as promoter regions, that are capable of effecting expression of such DNA fragments. Thus, an expression vector refers to a recombinant DNA or RNA construct, such as a plasmid, a phage, recombinant virus or other vector that, upon introduction into an appropriate host cell, results in expression of the cloned DNA. Appropriate expression vectors are well known to those of skill in the art and include those that are replicable in eukaryotic cells and/or prokaryotic cells and those that remain episomal or may integrate into the host cell genome.

As used herein, a promoter region refers to the portion of DNA of a gene that controls transcription of DNA to which it is operatively linked. The promoter region includes specific sequences of DNA that are sufficient for RNA polymerase recognition, binding and transcription initiation. This portion of the promoter region is referred to as the promoter. In addition, the promoter region includes sequences that modulate this recognition, binding and transcription initiation activity of the RNA polymerase. These sequences may be *cis* acting or may be responsive to *trans* acting factors. Promoters, depending upon the nature of the regulation, may be constitutive or regulated.

As used herein, a recombinant eukaryotic cell is a eukaryotic cell that contains heterologous DNA or RNA.

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As used herein, a recombinant or heterologous calcium channel refers to a calcium channel that contains one or more subunits that are encoded by heterologous DNA that has been introduced into and expressed in a eukaryotic cells that expresses the recombinant calcium channel. A recombinant calcium channel may also include subunits that are produced by DNA endogenous to the cell. In certain embodiments, the recombinant or heterologous calcium channel may contain only subunits that are encoded by heterologous DNA.

As used herein, "functional" with respect to a recombinant or heterologous calcium channel means that the channel is able to provide for and regulate entry of calcium channel-selective ions, including, but not limited to, Ca^{2+} or Ba^{2+} , in response to a stimulus and/or bind ligands with affinity for the channel. Preferably such calcium channel activity is distinguishable, such as electrophysiological, pharmacological and other means known to those of skill in the art, from any endogenous calcium channel activity that in the host cell.

As used herein, a peptide having an amino acid sequence substantially as set forth in a particular SEQ ID No. includes peptides that have the same function but may include minor variations in sequence, such as conservative amino acid changes or minor deletions or insertions that do not alter the activity of the peptide. The activity of a calcium channel receptor subunit peptide refers to its ability to form functional calcium channels with other such subunits.

As used herein, a physiological concentration of a compound is that which is necessary and sufficient for a biological process to occur. For example, a physiological concentration of a calcium channel-selective ion is a concentration of the calcium channel-selective ion necessary and sufficient to provide an inward current when the channels open.

As used herein, activity of a calcium channel refers to the movement of a calcium channel-selective ion through a

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calcium channel. Such activity may be measured by any method known to those of skill in the art, including, but not limited to, measurement of the amount of current which flows through the recombinant channel in response to a stimulus.

As used herein, a "functional assay" refers to an assay that identifies functional calcium channels. A functional assay, thus, is an assay to assess function.

As understood by those skilled in the art, assay methods for identifying compounds, such as antagonists and agonists, that modulate calcium channel activity, generally requires comparison to a control. One type of a "control" cell or "control" culture is a cell or culture that is treated substantially the same as the cell or culture exposed to the test compound except that the control culture is not exposed to the test compound. Another type of a "control" cell or "control" culture may be a cell or a culture of cells which are identical to the transfected cells except the cells employed for the control culture do not express functional calcium channels. In this situation, the response of test cell to the test compound is compared to the response (or lack of response) of the calcium channel-negative cell to the test compound, when cells or cultures of each type of cell are exposed to substantially the same reaction conditions in the presence of the compound being assayed. For example, in methods that use patch clamp electrophysiological procedures, the same cell can be tested in the presence and absence of the test compound, by changing the external solution bathing the cell as known in the art.

It is also understood that each of the subunits disclosed herein may be modified by making conservative amino acid substitutions and the resulting modified subunits are contemplated herein. Suitable conservative substitutions of amino acids are known to those of skill in this art and may be made generally without altering the biological activity of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-

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essential regions of a polypeptide do not substantially alter biological activity (see, e.g., Watson et al. *Molecular Biology of the Gene*, 4th Edition, 1987, The Bejacmin/Cummings Pub. co., p.224). Such substitutions are preferably, although not exclusively, made in accordance with those set forth in TABLE 1 as follows:

TABLE 1

Original residue	Conservative substitution
Ala (A)	Gly; Ser
Arg (R)	Lys
Asn (N)	Gln; His
Cys (C)	Ser
Gln (Q)	Asn
Glu (E)	Asp
Gly (G)	Ala; Pro
His (H)	Asn; Gln
Ile (I)	Leu; Val
Leu (L)	Ile; Val
Lys (K)	Arg; Gln; Glu
Met (M)	Leu; Tyr; Ile
Phe (F)	Met; Leu; Tyr
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr
Tyr (Y)	Trp; Phe
Val (V)	Ile; Leu

Other substitutions are also permissible and may be determined empirically or in accord with known conservative substitutions. Any such modification of the polypeptide may be effected by any means known to those of skill in this art. Mutation may be effected by any method known to those of skill in the art, including site-specific or site-directed mutagenesis of DNA encoding the protein and the use of DNA amplification methods using primers to introduce and amplify alterations in the DNA template.

Identification and isolation of DNA encoding human calcium channel subunits

Methods for identifying and isolating DNA encoding α_1 , α_2 , β and γ subunits of human calcium channels are provided.

Identification and isolation of such DNA may be accomplished by hybridizing, under appropriate conditions, at least low stringency whereby DNA that encodes the desired

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subunit is isolated, restriction enzyme-digested human DNA with a labeled probe having at least 14, preferably 16 or more nucleotides and derived from any contiguous portion of DNA having a sequence of nucleotides set forth herein by sequence identification number. Once a hybridizing fragment is identified in the hybridization reaction, it can be cloned employing standard cloning techniques known to those of skill in the art. Full-length clones may be identified by the presence of a complete open reading frame and the identity of the encoded protein verified by sequence comparison with the subunits provided herein and by functional assays to assess calcium channel-forming ability or other function. This method can be used to identify genomic DNA encoding the subunit or cDNA encoding splice variants of human calcium channel subunits generated by alternative splicing of the primary transcript of genomic subunit DNA. For instance, DNA, cDNA or genomic DNA, encoding a calcium channel subunit may be identified by hybridization to a DNA probe and characterized by methods known to those of skill in the art, such as restriction mapping and DNA sequencing, and compared to the DNA provided herein in order to identify heterogeneity or divergence in the sequences of the DNA. Such sequence differences may indicate that the transcripts from which the cDNA was produced result from alternative splicing of a primary transcript, if the non-homologous and homologous regions are clustered, or from a different gene if the non-homologous regions are distributed throughout the cloned DNA.

Any suitable method for isolating genes using the DNA provided herein may be used. For example, oligonucleotides corresponding to regions of sequence differences have been used to isolate, by hybridization, DNA encoding the full-length splice variant and can be used to isolate genomic clones. A probe, based on a nucleotide sequence disclosed herein, which encodes at least a portion of a subunit of a human calcium channel, such as a tissue-specific exon, may be used as a probe to clone related DNA, to clone a full-length

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cDNA clone or genomic clone encoding the human calcium channel subunit.

Labeled, including, but not limited to, radioactively or enzymatically labeled, RNA or single-stranded DNA of at least 14 substantially contiguous bases, preferably 16 or more, generally at least 30 contiguous bases of a nucleic acid which encodes at least a portion of a human calcium channel subunit, the sequence of which nucleic acid corresponds to a segment of a nucleic acid sequence disclosed herein by reference to a SEQ ID No. are provided. Such nucleic acid segments may be used as probes in the methods provided herein for cloning DNA encoding calcium channel subunits. See, generally, Sambrook et al. (1989) *Molecular Cloning: A Laboratory Manual*, 2nd Edition, Cold Spring Harbor Laboratory Press.

In addition, nucleic acid amplification techniques, which are well known in the art, can be used to locate splice variants of calcium channel subunits by employing oligonucleotides based on DNA sequences surrounding the divergent sequence primers for amplifying human RNA or genomic DNA. Size and sequence determinations of the amplification products can reveal splice variants. Furthermore, isolation of human genomic DNA sequences by hybridization can yield DNA containing multiple exons, separated by introns, that correspond to different splice variants of transcripts encoding human calcium channel subunits.

DNA encoding types and subtypes of each of the α_1 , α_2 , β and γ subunit of voltage-dependent human calcium channels has been cloned herein by nucleic acid amplification of cDNA from selected tissues or by screening human cDNA libraries prepared from isolated poly A+ mRNA from cell lines or tissue of human origin having such calcium channels. Among the sources of such cells or tissue for obtaining mRNA are human brain tissue or a human cell line of neural origin, such as a neuroblastoma cell line, human skeletal muscle or smooth muscle cells, and the like. Methods of preparing cDNA libraries are well known in the art [see generally Ausubel et al. (1987) *Current*

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Protocols in Molecular Biology, Wiley-Interscience, New York; and Davis et al. (1986) *Basic Methods in Molecular Biology*, Elsevier Science Publishing Co., New York].

Preferred regions from which to construct probes include 5' and/or 3' coding sequences, sequences predicted to encode transmembrane domains, sequences predicted to encode cytoplasmic loops, signal sequences, ligand-binding sites, and other functionally significant sequences (see Table, below). Either the full-length subunit-encoding DNA or fragments thereof can be used as probes, preferably labeled with suitable label means for ready detection. When fragments are used as probes, preferably the DNA sequences will be typically from the carboxyl-end-encoding portion of the DNA, and most preferably will include predicted transmembrane domain-encoding portions based on hydropathy analysis of the deduced amino acid sequence [see, e.g., Kyte and Doolittle [(1982) *J. Mol. Biol.* 167:105].

Riboprobes that specific for human calcium channel subunit types or subtypes have been prepared. These probes are useful for identifying expression of particular subunits in selected tissues and cells. The regions from which the probes were prepared were identified by comparing the DNA and amino acid sequences of all known α or β subunit subtypes. Regions of least homology, preferably human-derived sequences, and generally about 250 to about 600 nucleotides were selected. Numerous riboprobes for α and β subunits have been prepared; some of these are listed in the following Table.

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TABLE 2
SUMMARY OF RNA PROBES

SUBUNIT SPECIFICITY	NUCLEOTIDE POSITION	PROBE NAME	PROBE TYPE	ORIENTATION
$\alpha 1A$ generic	3357-3840	pGEM7Z $\alpha 1A$ *	riboprobe	n/a
	761-790	SE700	oligo	antisense
	3440-3464	SE718	oligo	antisense
	3542-3565	SE724	oligo	sense
$\alpha 1B$ generic	3091-3463	pGEM7Z $\alpha 1B_{\text{cyt}}$	riboprobe	n/a
	6635-6858	pGEM7Z $\alpha 1B_{\text{cooh}}$	riboprobe	n/a
$\alpha 1B$ -1 specific	6490-6676	pCRII $\alpha 1B$ -1/187	riboprobe	n/a
$\alpha 1E$ generic	3114-3462	pGEM7Z $\alpha 1E$	riboprobe	n/a
$\alpha 2b$	1321-1603	pCRII $\alpha 2b$	riboprobe	n/a
β generic(?)	212-236	SE300	oligo	antisense
$\beta 1$ generic	1267-1291	SE301	oligo	antisense
$\beta 1$ -2 specific	1333-1362	SE17	oligo	antisense
	1682-1706	SE23	oligo	sense
	2742-2766	SE43	oligo	antisense
	27-56	SE208	oligo	antisense
	340-364	SE274	oligo	antisense
	340-364	SE275	oligo	sense
$\beta 3$ specific	1309-1509		riboprobe	n/a
$\beta 4$ specific	1228-1560		riboprobe	n/a

* The pGEM series are available from Promega, Madison WI; see also, U.S. Patent No. 4,766,072.

The above-noted nucleotide regions are also useful in selecting regions of the protein for preparation of subunit-specific antibodies, discussed below.

The DNA clones and fragments thereof provided herein thus can be used to isolate genomic clones encoding each subunit and to isolate any splice variants by hybridization screening of libraries prepared from different human tissues. Nucleic acid amplification techniques, which are well known in the art, can also be used to locate DNA encoding splice variants

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of human calcium channel subunits. This is accomplished by employing oligonucleotides based on DNA sequences surrounding divergent sequence(s) as primers for amplifying human RNA or genomic DNA. Size and sequence determinations of the amplification products can reveal the existence of splice variants. Furthermore, isolation of human genomic DNA sequences by hybridization can yield DNA containing multiple exons, separated by introns, that correspond to different splice variants of transcripts encoding human calcium channel subunits.

Once DNA encoding a calcium channel subunit is isolated, ribonuclease (RNase) protection assays can be employed to determine which tissues express mRNA encoding a particular calcium channel subunit or variant. These assays provide a sensitive means for detecting and quantitating an RNA species in a complex mixture of total cellular RNA. The subunit DNA is labeled and hybridized with cellular RNA. If complementary mRNA is present in the cellular RNA, a DNA-RNA hybrid results. The RNA sample is then treated with RNase, which degrades single-stranded RNA. Any RNA-DNA hybrids are protected from RNase degradation and can be visualized by gel electrophoresis and autoradiography. *In situ* hybridization techniques can also be used to determine which tissues express mRNA encoding a particular calcium channel subunit. The labeled subunit DNAs are hybridized to different tissue slices to visualize subunit mRNA expression.

With respect to each of the respective subunits (α_1 , α_2 , β or γ) of human calcium channels, once the DNA encoding the channel subunit was identified by a nucleic acid screening method, the isolated clone was used for further screening to identify overlapping clones. Some of the cloned DNA fragments can and have been subcloned into an appropriate vector such as pIBI24/25 (IBI, New Haven, CT), M13mp18/19, pGEM4, pGEM3, pGEM7Z, pSP72 and other such vectors known to those of skill in this art, and characterized by DNA sequencing and restriction enzyme mapping. A sequential series of

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overlapping clones may thus be generated for each of the subunits until a full-length clone can be prepared by methods, known to those of skill in the art, that include identification of translation initiation (start) and translation termination (stop) codons. For expression of the cloned DNA, the 5' noncoding region and other transcriptional and translational control regions of such a clone may be replaced with an efficient ribosome binding site and other regulatory regions as known in the art. Other modifications of the 5' end, known to those of skill in the art, that may be required to optimize translation and/or transcription efficiency may also be effected, if deemed necessary.

Examples II-VIIII, below, describe in detail the cloning of each of the various subunits of a human calcium channel as well as subtypes and splice variants, including tissue-specific variants thereof. In the few instances in which partial sequences of a subunit are disclosed, it is well within the skill of the art, in view of the teaching herein, to obtain the corresponding full-length clones and sequence thereof encoding the subunit, subtype or splice variant thereof using the methods described above and exemplified below.

Identification and isolation of DNA encoding α_1 subunits

A number of voltage-dependent calcium channel α_1 subunit genes, which are expressed in the human CNS and in other tissues, have been identified and have been designated as α_{1A} , α_{1B} (or VDCC IV), α_{1C} (or VDCC II), α_{1D} (or VDCC III) and α_{1E} . DNA, isolated from a human neural cDNA library, that encodes each of the subunit types has been isolated. DNA encoding subtypes of each of the types, which arise as splice variants are also provided. Subtypes are herein designated, for example, as α_{1B-1} , α_{1B-2} .

The α_1 subunits types A B, C, D and E of voltage-dependent calcium channels, and subtypes thereof, differ with respect to sensitivity to known classes of calcium channel

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agonists and antagonists, such as DHPs, phenylalkylamines, omega conotoxin (ω -CgTx), the funnel web spider toxin ω -Aga-IV, and pyrazonoylguanidines. These subunit types also appear to differ in the holding potential and in the kinetics of currents produced upon depolarization of cell membranes containing calcium channels that include different types of α_1 subunits.

DNA that encodes an α_1 subunit that binds to at least one compound selected from among dihydropyridines, phenylalkylamines, ω -CgTx, components of funnel web spider toxin, and pyrazonoylguanidines is provided. For example, the α_{1B} subunit provided herein appears to specifically interact with ω -CgTx in N-type channels, and the α_{1D} subunit provided herein specifically interacts with DHPs in L-type channels.

**Identification and isolation of DNA
encoding the α_{1D} human calcium channel
subunit**

The α_{1D} subunit cDNA has been isolated using fragments of the rabbit skeletal muscle calcium channel α_1 subunit cDNA as a probe to screen a cDNA library of a human neuroblastoma cell line, IMR32, to obtain clone $\alpha 1.36$. This clone was used as a probe to screen additional IMR32 cell cDNA libraries to obtain overlapping clones, which were then employed for screening until a sufficient series of clones to span the length of the nucleotide sequence encoding the human α_{1D} subunit was obtained. Full-length clones encoding α_{1D} were constructed by ligating portions of partial α_{1D} clones as described in Example II. SEQ ID No. 1 shows the 7,635 nucleotide sequence of the cDNA encoding the α_{1D} subunit. There is a 6,483 nucleotide sequence reading frame which encodes a sequence of 2,161 amino acids (as set forth in SEQ ID No. 1).

SEQ ID No. 2 provides the sequence of an alternative exon encoding the IS6 transmembrane domain [see Tanabe, T., et al. (1987) Nature 328:313-318 for a description of transmembrane domain terminology] of the α_{1D} subunit.

SEQ ID No. 1 also shows the 2,161 amino acid sequence deduced from the human neuronal calcium channel α_{1D} subunit

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DNA. Based on the amino acid sequence, the α_{1D} protein has a calculated Mr of 245,163. The α_{1D} subunit of the calcium channel contains four putative internal repeated sequence regions. Four internally repeated regions represent 24 putative transmembrane segments, and the amino- and carboxyl-termini extend intracellularly.

The α_{1D} subunit has been shown to mediate DHP-sensitive, high-voltage-activated, long-lasting calcium channel activity. This calcium channel activity was detected when oocytes were co-injected with RNA transcripts encoding an α_{1D} and $\beta_{1,2}$ or α_{1D} , α_{2B} and $\beta_{1,2}$ subunits. This activity was distinguished from Ba^{2+} currents detected when oocytes were injected with RNA transcripts encoding the $\beta_{1,2} + \alpha_{2B}$ subunits. These currents pharmacologically and biophysically resembled Ca^{2+} currents reported for uninjected oocytes.

**Identification and isolation of DNA
encoding the α_{1A} human calcium channel
subunit**

Biological material containing DNA encoding a portion of the α_{1A} subunit had been deposited in the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852 U.S.A. under the terms of the Budapest Treaty on the International Recognition of Deposits of Microorganisms for Purposes of Patent Procedure and the Regulations promulgated under this Treaty. Samples of the deposited material are and will be available to industrial property offices and other persons legally entitled to receive them under the terms of the Treaty and Regulations and otherwise in compliance with the patent laws and regulations of the United States of America and all other nations or international organizations in which this application, or an application claiming priority of this application, is filed or in which any patent granted on any such application is granted.

A portion of an α_{1A} subunit is encoded by an approximately 3 kb insert in λ gt10 phage designated $\alpha 1.254$ in *E. coli* host strain NM514. A phage lysate of this material has been deposited as at the American Type Culture Collection under

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ATCC Accession No. 75293, as described above. DNA encoding α_{1A} may also be identified by screening with a probe prepared from DNA that has SEQ ID No. 21:

5' CTCAGTACCATCTCTGATACCAGCCCCA 3'.

α_{1A} splice variants have been obtained. The sequences of two α_{1A} splice variants, α_{1A-1} and α_{1A-2} are set forth in SEQ. ID Nos. 22 and 23. Other splice variants may be obtained by screening a human library as described above or using all or a portion of the sequences set forth in SEQ ID Nos. 22 and 23.

**Identification and isolation of DNA
encoding the α_{1B} human calcium channel
subunit**

DNA encoding the α_{1B} subunit was isolated by screening a human basal ganglia cDNA library with fragments of the rabbit skeletal muscle calcium channel α_1 subunit-encoding cDNA. A portion of one of the positive clones was used to screen an IMR32 cell cDNA library. Clones that hybridized to the basal ganglia DNA probe were used to further screen an IMR32 cell cDNA library to identify overlapping clones that in turn were used to screen a human hippocampus cDNA library. In this way, a sufficient series of clones to span nearly the entire length of the nucleotide sequence encoding the human α_{1B} subunit was obtained. Nucleic acid amplification of specific regions of the IMR32 cell α_{1B} mRNA yielded additional segments of the α_{1B} coding sequence.

A full-length α_{1B} DNA clone was constructed by ligating portions of the partial cDNA clones as described in Example II.C. SEQ ID Nos. 7 and 8 show the nucleotide sequences of DNA clones encoding the α_{1B} subunit as well as the deduced amino acid sequences. The α_{1B} subunit encoded by SEQ ID No. 7 is referred to as the α_{1B-1} subunit to distinguish it from another α_{1B} subunit, α_{1B-2} , encoded by the nucleotide sequence shown as SEQ ID No. 8, which is derived from alternative splicing of the α_{1B} subunit transcript.

Nucleic acid amplification of IMR32 cell mRNA using oligonucleotide primers designed according to nucleotide

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sequences within the α_{1B-1} -encoding DNA has identified variants of the α_{1B} transcript that appear to be splice variants because they contain divergent coding sequences.

**Identification and isolation of DNA
encoding the α_{1C} human calcium channel
subunit**

Numerous α_{1C} -specific DNA clones were isolated. Characterization of the sequence revealed the α_{1C} coding sequence, the α_{1C} initiation of translation sequence, and an alternatively spliced region of α_{1C} . Alternatively spliced variants of the α_{1C} subunit have been identified. SEQ ID No. 3 sets forth DNA encoding a substantial portion of an α_{1C} subunit. The DNA sequences set forth in SEQ ID No. 4 and No. 5 encode two possible amino terminal ends of the α_{1C} protein. SEQ ID No. 6 encodes an alternative exon for the IV S3 transmembrane domain. The sequences of substantial portions of two α_{1C} splice variants, designated α_{1C-1} and α_{1C-2} , are set forth in SEQ ID NOS. 3 and 36, respectively.

The isolation and identification of DNA clones encoding portions of the α_{1C} subunit is described in detail in Example II.

**Identification and isolation of DNA
encoding the α_{1E} human calcium channel
subunit**

DNA encoding α_{1E} human calcium channel subunits have been isolated from an oligo dT-primed human hippocampus library. The resulting clones, which are splice variants, were designated α_{1E-1} and α_{1E-3} . The subunit designated α_{1E-1} has the amino acid sequence set forth in SEQ ID No. 24, and a subunit designated α_{1E-3} has the amino acid sequence set forth in SEQ ID No. 25. These splice variants differ by virtue of a 57 base pair insert between nucleotides 2405 and 2406 of SEQ. ID No. 24.

The α_{1E} subunits provided herein appear to participate in the formation of calcium channels that have properties of high-voltage activated calcium channels and low-voltage activated channels. These channels are rapidly inactivating

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compared to other high voltage-activated calcium channels. In addition these channels exhibit pharmacological profiles that are similar to voltage-activated channels, but are also sensitive to DHPS and ω -Aga-IVA, which block certain high voltage activated channels. Additional details regarding the electrophysiology and pharmacology of channels containing α_{1E} subunits is provided in Example VII. F.

**Identification and isolation of DNA
encoding encoding additional α_1 human
calcium channel subunit types and
subtypes**

DNA encoding additional α_1 subunits can be isolated and identified using the DNA provided herein as described for the α_{1A} , α_{1B} , α_{1C} , α_{1D} and α_{1E} subunits or using other methods known to those of skill in the art. In particular, the DNA provided herein may be used to screen appropriate libraries to isolate related DNA. Full-length clones can be constructed using methods, such as those described herein, and the resulting subunits characterized by comparison of their sequences and electrophysiological and pharmacological properties with the subunits exemplified herein.

**Identification and isolation of DNA encoding β
human calcium channel subunits**

DNA encoding β_1

To isolate DNA encoding the β_1 subunit, a human hippocampus cDNA library was screened by hybridization to a DNA fragment encoding a rabbit skeletal muscle calcium channel β subunit. A hybridizing clone was selected and was in turn used to isolate overlapping clones until the overlapping clones encompassing DNA encoding the entire the human calcium channel β subunit were isolated and sequenced.

Five alternatively spliced forms of the human calcium channel β_1 subunit have been identified and DNA encoding a number of forms have been isolated. These forms are designated $\beta_{1.1}$, expressed in skeletal muscle, $\beta_{1.2}$, expressed in the CNS, $\beta_{1.3}$, also expressed in the in the CNS, $\beta_{1.4}$, expressed in aorta tissue and HEK 293 cells, and $\beta_{1.5}$.

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expressed in HEK 293 cells. Full-length DNA clones encoding the β_{1-2} and β_{1-3} subunits have been constructed. The subunits β_{1-1} , β_{1-2} , β_{1-4} and β_{1-5} have been identified by nucleic acid amplification analysis as alternatively spliced forms of the β subunit. Sequences of the β_1 splice variants are set forth in SEQ ID Nos. 9, 10 and 33-35.

DNA encoding β_2

DNA encoding the β_2 splice variants has been obtained. These splice variants include β_{2C} - β_{2E} . Splice variants β_{2C} - β_{2E} include all of sequence set forth in SEQ ID No. 26, except for the portion at the 5' end (up to nucleotide 182), which differs among splice variants. The sequence set forth in SEQ ID No. 26 encodes β_{2D} . Additional splice variants may be isolated using the methods described herein and oligonucleotides including all or portions of the DNA set forth in SEQ ID No. 26 or may be prepared or obtained as described in the Examples. The sequences of β_2 splice variants β_{2C} and β_{2E} are set forth in SEQ ID Nos. 37 and 38, respectively.

DNA encoding β_3

DNA encoding the β_3 subunit and any splice variants thereof may be isolated by screening a library, as described above for the β_1 subunit, using DNA probes prepared according to SEQ ID Nos. 19, 20 or using all or a portion of the deposited β_3 clone plasmid $\beta 1.42$ (ATCC Accession No. 69048).

The *E. coli* host containing plasmid $\beta 1.42$ that includes DNA encoding a β_3 subunit has been deposited as ATCC Accession No. 69048 in the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852 U.S.A. under the terms of the Budapest Treaty on the International Recognition of Deposits of Microorganisms for Purposes of Patent Procedure and the Regulations promulgated under this Treaty. Samples of the deposited material are and will be available to industrial property offices and other persons legally entitled to receive them under the terms of the Treaty and Regulations and otherwise in compliance with the patent laws and regulations

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of the United States of America and all other nations or international organizations in which this application, or an application claiming priority of this application, is filed or in which any patent granted on any such application is granted.

The β , encoding plasmid is designated β 1.42. The plasmid contains a 2.5 kb EcoRI fragment encoding β , inserted into vector pGem[®]7zF(+) and has been deposited in *E. coli* host strain DH5 α . The sequences of β , splice variants, designated β_{1-1} and β_{1-2} are set forth in SEQ ID Nos. 19 and 20, respectively.

Identification and isolation of DNA encoding the α 2 human calcium channel subunit

DNA encoding a human neuronal calcium channel α , subunit was isolated in a manner substantially similar to that used for isolating DNA encoding an α , subunit, except that a human genomic DNA library was probed under low and high stringency conditions with a fragment of DNA encoding the rabbit skeletal muscle calcium channel α , subunit. The fragment included nucleotides having a sequence corresponding to the nucleotide sequence between nucleotides 43 and 272 inclusive of rabbit back skeletal muscle calcium channel α , subunit cDNA as disclosed in PCT International Patent Application Publication No. WO 89/09834, which corresponds to U.S. Application Serial No. 07/620,520 (now allowed U.S. Application Serial No. 07/914,231), which is a continuation-in-part of United States Serial No. 176,899, filed April 4, 1988.

Example IV describes the isolation of DNA clones encoding α , subunits of a human calcium channel from a human DNA library using genomic DNA and cDNA clones, identified by hybridization to the genomic DNA, as probes.

SEQ ID Nos. 11 and 29-32 show the sequence of DNA encoding α , subunits. As described in Example V, nucleic acid amplification analysis of RNA from human skeletal muscle, brain tissue and aorta using oligonucleotide primers specific for a region of the human neuronal α , subunit cDNA that

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diverges from the rabbit skeletal muscle calcium channel α_2 subunit cDNA identified splice variants of the human calcium channel α_2 subunit transcript.

Identification and isolation of DNA encoding γ human calcium channel subunits

DNA encoding a portion of a human neuronal calcium channel γ subunit has been isolated as described in detail in Example VI. SEQ ID No. 14 shows the nucleotide sequence at the 3'-end of this DNA which includes a reading frame encoding a sequence of 43 amino acid residues. Since the portion that has been obtained is homologous to the rabbit clone, described in allowed co-owned U.S. Application Serial No. 07/482,384, the remainder of the clone can be obtained using routine methods.

Antibodies

Antibodies, monoclonal or polyclonal, specific for calcium channel subunit subtypes or for calcium channel types can be prepared employing standard techniques, known to those of skill in the art, using the subunit proteins or portions thereof as antigens. Anti-peptide and anti-fusion protein antibodies can be used [see, for example, Bahouth et al. (1991) *Trends Pharmacol. Sci.* 12:338-343; *Current Protocols in Molecular Biology* (Ausubel et al., eds.) John Wiley and Sons, New York (1984)]. Factors to consider in selecting portions of the calcium channel subunits for use as immunogens (as either a synthetic peptide or a recombinantly produced bacterial fusion protein) include antigenicity accessibility (i.e., extracellular and cytoplasmic domains), uniqueness to the particular subunit, and other factors known to those of skill in this art.

The availability of subunit-specific antibodies makes possible the application of the technique of immunohistochemistry to monitor the distribution and expression density of various subunits (e.g., in normal vs diseased brain tissue). Such antibodies could also be employed in diagnostic, such as LES diagnosis, and therapeutic

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applications, such as using antibodies that modulate activities of calcium channels.

The antibodies can be administered to a subject employing standard methods, such as, for example, by intraperitoneal, intramuscular, intravenous, or subcutaneous injection, implant or transdermal modes of administration, and the like. One of skill in the art can empirically determine dose forms, treatment regimens, etc., depending on the mode of administration employed.

Subunit-specific monoclonal antibodies and polyclonal antisera have been prepared. The regions from which the antigens were identified by comparing the DNA and amino acid sequences of all known α or β subunit subtypes. Regions of least homology, preferably human-derived sequences were selected. The selected regions or fusion proteins containing the selected regions are used as immunogens. Hydrophobicity analyses of residues in selected protein regions and fusion proteins are also performed; regions of high hydrophobicity are avoided. Also, and more importantly, when preparing fusion proteins in bacterial hosts, rare codons are avoided. In particular, inclusion of 3 or more successive rare codons in a selected host is avoided. Numerous antibodies, polyclonal and monoclonal, specific for α or β subunits types or subtypes have been prepared; some of these are listed in the following Table. Exemplary antibodies and peptide antigens used to prepare the antibodies are set forth in the following Table:

TABLE 3

SPECIFICITY	AMINO ACID NUMBER	ANTIGEN NAME	ANTIBODY TYPE
$\alpha 1$ generic	112-140	peptide 1A#1	polyclonal
$\alpha 1$ generic	1420-1447	peptide 1A#2	polyclonal
$\alpha 1A$ generic	1048-1208	$\alpha 1A\#2$ (b) GST fusion	polyclonal
			monoclonal
$\alpha 1B$ generic	983-1106	$\alpha 1B\#2$ (b) GST fusion	polyclonal
			monoclonal

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α 1B-1	2164-2339	α 1B-1#3 GST fusion	polyclonal
α 1B-2	2164-2237	α 1B-2#4 GST fusion	polyclonal
α 1E generic	985-1004 (α 1E-3)	α 1E#2(a) GST fusion	polyclonal

* GST gene fusion system is available from Pharmacia; see also, Smith et al. (1988) *Gene* 67:31. The system provides pGEX plasmids that are designed for inducible, high-level expression of genes or gene fragments as fusions with *Schistosoma japonicum* GST. Upon expression in a bacterial host, the resulting fusion proteins are purified from bacterial lysates by affinity chromatography.

The GST fusion proteins are each specific for the cytoplasmic loop region IIS6-IIS1, which is a region of low subtype homology for all subtypes, including α_{1c} and α_{1D} , for which similar fusions and antisera can be prepared.

Preparation of recombinant eukaryotic cells containing DNA encoding heterologous calcium channel subunits

DNA encoding one or more of the calcium channel subunits or a portion of a calcium channel subunit may be introduced into a host cell for expression or replication of the DNA. Such DNA may be introduced using methods described in the following examples or using other procedures well known to those skilled in the art. Incorporation of cloned DNA into a suitable expression vector, transfection of eukaryotic cells with a plasmid vector or a combination of plasmid vectors, each encoding one or more distinct genes or with linear DNA, and selection of transfected cells are also well known in the art [see, e.g., Sambrook et al. (1989) *Molecular Cloning: A Laboratory Manual, Second Edition*, Cold Spring Harbor Laboratory Press]. Cloned full-length DNA encoding any of the subunits of a human calcium channel may be introduced into a plasmid vector for expression in a eukaryotic cell. Such DNA may be genomic DNA or cDNA. Host cells may be transfected with one or a combination of the plasmids, each of which encodes at least one calcium channel subunit. Alternatively, host cells may be transfected with linear DNA using methods well known to those of skill in the art.

While the DNA provided herein may be expressed in any eukaryotic cell, including yeast cells such as *P. pastoris*

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[see, e.g., Cregg et al. (1987) *Bio/Technology* 5:479], mammalian expression systems for expression of the DNA encoding the human calcium channel subunits provided herein are preferred.

The heterologous DNA may be introduced by any method known to those of skill in the art, such as transfection with a vector encoding the heterologous DNA. Particularly preferred vectors for transfection of mammalian cells are the pSV2dhfr expression vectors, which contain the SV40 early promoter, mouse dhfr gene, SV40 polyadenylation and splice sites and sequences necessary for maintaining the vector in bacteria, cytomegalovirus (CMV) promoter-based vectors such as pCDNA1, or pcDNA-amp and MMTV promoter-based vectors. DNA encoding the human calcium channel subunits has been inserted in the vector pCDNA1 at a position immediately following the CMV promoter. The vector pCDNA1 is presently preferred.

Stably or transiently transfected mammalian cells may be prepared by methods known in the art by transfecting cells with an expression vector having a selectable marker gene such as the gene for thymidine kinase, dihydrofolate reductase, neomycin resistance or the like, and, for transient transfection, growing the transfected cells under conditions selective for cells expressing the marker gene. Functional voltage-dependent calcium channels have been produced in HEK 293 cells transfected with a derivative of the vector pCDNA1 that contains DNA encoding a human calcium channel subunit.

The heterologous DNA may be maintained in the cell as an episomal element or may be integrated into chromosomal DNA of the cell. The resulting recombinant cells may then be cultured or subcultured (or passaged, in the case of mammalian cells) from such a culture or a subculture thereof. Methods for transfection, injection and culturing recombinant cells are known to the skilled artisan. Eukaryotic cells in which DNA or RNA may be introduced, include any cells that are transfectable by such DNA or RNA or into which such DNA may be injected. Virtually any eukaryotic cell can serve as a

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vehicle for heterologous DNA. Preferred cells are those that can also express the DNA and RNA and most preferred cells are those that can form recombinant or heterologous calcium channels that include one or more subunits encoded by the heterologous DNA. Such cells may be identified empirically or selected from among those known to be readily transfected or injected. Preferred cells for introducing DNA include those that can be transiently or stably transfected and include, but are not limited to, cells of mammalian origin, such as COS cells, mouse L cells, CHO cells, human embryonic kidney cells, African green monkey cells and other such cells known to those of skill in the art, amphibian cells, such as *Xenopus laevis* oocytes, or those of yeast such as *Saccharomyces cerevisiae* or *Pichia pastoris*. Preferred cells for expressing injected RNA transcripts or cDNA include *Xenopus laevis* oocytes. Cells that are preferred for transfection of DNA are those that can be readily and efficiently transfected. Such cells are known to those of skill in the art or may be empirically identified. Preferred cells include DG44 cells and HEK 293 cells, particularly HEK 293 cells that can be frozen in liquid nitrogen and then thawed and regrown. Such HEK 293 cells are described, for example in U.S. Patent No. 5,024,939 to Gorman [see, also Stillman et al. (1985) *Mol. Cell. Biol.* 5:2051-2060].

The cells may be used as vehicles for replicating heterologous DNA introduced therein or for expressing the heterologous DNA introduced therein. In certain embodiments, the cells are used as vehicles for expressing the heterologous DNA as a means to produce substantially pure human calcium channel subunits or heterologous calcium channels. Host cells containing the heterologous DNA may be cultured under conditions whereby the calcium channels are expressed. The calcium channel subunits may be purified using protein purification methods known to those of skill in the art. For example, antibodies, such as those provided herein, that specifically bind to one or more of the subunits may be used

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for affinity purification of the subunit or calcium channels containing the subunits.

Substantially pure subunits of a human calcium channel α_1 subunits of a human calcium channel, α_2 subunits of a human calcium channel, β subunits of a human calcium channel and γ subunits of a human calcium channel are provided. Substantially pure isolated calcium channels that contain at least one of the human calcium channel subunits are also provided. Substantially pure calcium channels that contain a mixture of one or more subunits encoded by the host cell and one or more subunits encoded by heterologous DNA or RNA that has been introduced into the cell are also provided. Substantially pure subtype- or tissue-type specific calcium channels are also provided.

In other embodiments, eukaryotic cells that contain heterologous DNA encoding at least one of an α_1 subunit of a human calcium channel, an α_2 subunit of a human calcium channel, a β subunit of a human calcium channel and a γ subunit of a human calcium channel are provided. In accordance with one preferred embodiment, the heterologous DNA is expressed in the eukaryotic cell and preferably encodes a human calcium channel α_1 subunit.

Expression of heterologous calcium channels: electrophysiology and pharmacology

Electrophysiological methods for measuring calcium channel activity are known to those of skill in the art and are exemplified herein. Any such methods may be used in order to detect the formation of functional calcium channels and to characterize the kinetics and other characteristics of the resulting currents. Pharmacological studies may be combined with the electrophysiological measurements in order to further characterize the calcium channels.

With respect to measurement of the activity of functional heterologous calcium channels, preferably, endogenous ion channel activity and, if desired, heterologous channel activity of channels that do not contain the desired subunits,

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of a host cell can be inhibited to a significant extent by chemical, pharmacological and electrophysiological means, including the use of differential holding potential, to increase the S/N ratio of the measured heterologous calcium channel activity.

Thus, various combinations of subunits encoded by the DNA provided herein are introduced into eukaryotic cells. The resulting cells can be examined to ascertain whether functional channels are expressed and to determine the properties of the channels. In particularly preferred aspects, the eukaryotic cell which contains the heterologous DNA expresses it and forms a recombinant functional calcium channel activity. In more preferred aspects, the recombinant calcium channel activity is readily detectable because it is a type that is absent from the untransfected host cell or is of a magnitude and/or pharmacological properties or exhibits biophysical properties not exhibited in the untransfected cell.

The eukaryotic cells can be transfected with various combinations of the subunit subtypes provided herein. The resulting cells will provide a uniform population of calcium channels for study of calcium channel activity and for use in the drug screening assays provided herein. Experiments that have been performed have demonstrated the inadequacy of prior classification schemes.

Preferred among transfected cells is a recombinant eukaryotic cell with a functional heterologous calcium channel. The recombinant cell can be produced by introduction of and expression of heterologous DNA or RNA transcripts encoding an α_1 subunit of a human calcium channel, more preferably also expressing, a heterologous DNA encoding a β subunit of a human calcium channel and/or heterologous DNA encoding an α_2 subunit of a human calcium channel. Especially preferred is the expression in such a recombinant cell of each of the α_1 , β and α_2 subunits encoded by such heterologous DNA or RNA transcripts, and optionally expression of heterologous

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DNA or an RNA transcript encoding a γ subunit of a human calcium channel. The functional calcium channels may preferably include at least an α_1 subunit and a β subunit of a human calcium channel. Eukaryotic cells expressing these two subunits and also cells expressing additional subunits, have been prepared by transfection of DNA and by injection of RNA transcripts. Such cells have exhibited voltage-dependent calcium channel activity attributable to calcium channels that contain one or more of the heterologous human calcium channel subunits. For example, eukaryotic cells expressing heterologous calcium channels containing an α_2 subunit in addition to the α_1 subunit and a β subunit have been shown to exhibit increased calcium selective ion flow across the cellular membrane in response to depolarization, indicating that the α_2 subunit may potentiate calcium channel function. Cells that have been co-transfected with increasing ratios of α_2 to α_1 and the activity of the resulting calcium channels has been measured. The results indicate that α_2 , increasing the amount of α_2 -encoding DNA relative to the other transfected subunits increases calcium channel activity.

Eukaryotic cells which express heterologous calcium channels containing at least a human α_1 subunit, a human β subunit and a human α_2 subunit are preferred. Eukaryotic cells transformed with a composition containing cDNA or an RNA transcript that encodes an α_1 subunit alone or in combination with a β and/or an α_2 subunit may be used to produce cells that express functional calcium channels. Since recombinant cells expressing human calcium channels containing all of the human subunits encoded by the heterologous cDNA or RNA are especially preferred, it is desirable to inject or transfect such host cells with a sufficient concentration of the subunit-encoding nucleic acids to form calcium channels that contain the human subunits encoded by heterologous DNA or RNA. The precise amounts and ratios of DNA or RNA encoding the subunits may be empirically determined and optimized for a

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particular combination of subunits, cells and assay conditions.

In particular, mammalian cells have been transiently and stably transfected with DNA encoding one or more human calcium channel subunits. Such cells express heterologous calcium channels that exhibit pharmacological and electrophysiological properties that can be ascribed to human calcium channels. Such cells, however, represent homogeneous populations and the pharmacological and electrophysiological data provides insights into human calcium channel activity heretofore unattainable. For example, HEK cells that have been transiently transfected with DNA encoding the α_{1B-1} , α_{2b} , and β_{1-3} subunits. The resulting cells transiently express these subunits, which form calcium channels that have properties that appear to be a pharmacologically distinct class of voltage-activated calcium channels distinct from those of L-, N-, T- and P-type channels. The observed α_{1B} currents were insensitive to drugs and toxins previously used to define other classes of voltage-activated calcium channels.

HEK cells that have been transiently transfected with DNA encoding α_{1B-1} , α_{2b} , and β_{1-2} express heterologous calcium channels that exhibit sensitivity to ω -conotoxin and currents typical of N-type channels. It has been found that alteration of the molar ratios of α_{1B-1} , α_{2b} and β_{1-2} introduced into the cells in order to achieve equivalent mRNA levels significantly increased the number of receptors per cell, the current density, and affected the K_d for ω -conotoxin.

The electrophysiological properties of these channels produced from α_{1B-1} , α_{2b} , and β_{1-2} was compared with those of channels produced by transiently transfecting HEK cells with DNA encoding α_{1B-1} , α_{2b} and β_{1-3} . The channels exhibited similar voltage dependence of activation, substantially identical voltage dependence, similar kinetics of activation and tail currents that could be fit by a single exponential. The voltage dependence of the kinetics of inactivation was significantly different at all voltages examined.

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In certain embodiments, the eukaryotic cell with a heterologous calcium channel is produced by introducing into the cell a first composition, which contains at least one RNA transcript that is translated in the cell into a subunit of a human calcium channel. In preferred embodiments, the subunits that are translated include an α_1 subunit of a human calcium channel. More preferably, the composition that is introduced contains an RNA transcript which encodes an α_1 subunit of a human calcium channel and also contains (1) an RNA transcript which encodes a β subunit of a human calcium channel and/or (2) an RNA transcript which encodes an α_2 subunit of a human calcium channel. Especially preferred is the introduction of RNA encoding an α_1 , a β and an α_2 human calcium channel subunit, and, optionally, a γ subunit of a human calcium channel. Methods for *in vitro* transcription of a cloned DNA and injection of the resulting RNA into eukaryotic cells are well known in the art. Transcripts of any of the full-length DNA encoding any of the subunits of a human calcium channel may be injected alone or in combination with other transcripts into eukaryotic cells for expression in the cells. Amphibian oocytes are particularly preferred for expression of *in vitro* transcripts of the human calcium channel subunit cDNA clones provided herein. Amphibian oocytes that express functional heterologous calcium channels have been produced by this method.

Assays and Clinical uses of the cells and calcium channels

Assays

Assays for identifying compounds that modulate calcium channel activity

Among the uses for eukaryotic cells which recombinantly express one or more subunits are assays for determining whether a test compound has calcium channel agonist or antagonist activity. These eukaryotic cells may also be used to select from among known calcium channel agonists and antagonists those exhibiting a particular calcium channel

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subtype specificity and to thereby select compounds that have potential as disease- or tissue-specific therapeutic agents.

In vitro methods for identifying compounds, such as calcium channel agonist and antagonists, that modulate the activity of calcium channels using eukaryotic cells that express heterologous human calcium channels are provided.

In particular, the assays use eukaryotic cells that express heterologous human calcium channel subunits encoded by heterologous DNA provided herein, for screening potential calcium channel agonists and antagonists which are specific for human calcium channels and particularly for screening for compounds that are specific for particular human calcium channel subtypes. Such assays may be used in conjunction with methods of rational drug design to select among agonists and antagonists, which differ slightly in structure, those particularly useful for modulating the activity of human calcium channels, and to design or select compounds that exhibit subtype- or tissue- specific calcium channel antagonist and agonist activities. These assays should accurately predict the relative therapeutic efficacy of a compound for the treatment of certain disorders in humans. In addition, since subtype-and tissue-specific calcium channel subunits are provided, cells with tissue- specific or subtype-specific recombinant calcium channels may be prepared and used in assays for identification of human calcium channel tissue- or subtype-specific drugs.

Desirably, the host cell for the expression of calcium channel subunits does not produce endogenous calcium channel subunits of the type or in an amount that substantially interferes with the detection of heterologous calcium channel subunits in ligand binding assays or detection of heterologous calcium channel function, such as generation of calcium current, in functional assays. Also, the host cells preferably should not produce endogenous calcium channels which detectably interact with compounds having, at physiological concentrations (generally nanomolar or picomolar

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concentrations), affinity for calcium channels that contain one or all of the human calcium channel subunits provided herein.

With respect to ligand binding assays for identifying a compound which has affinity for calcium channels, cells are employed which express, preferably, at least a heterologous α_1 subunit. Transfected eukaryotic cells which express at least an α_1 subunit may be used to determine the ability of a test compound to specifically bind to heterologous calcium channels by, for example, evaluating the ability of the test compound to inhibit the interaction of a labeled compound known to specifically interact with calcium channels. Such ligand binding assays may be performed on intact transfected cells or membranes prepared therefrom.

The capacity of a test compound to bind to or otherwise interact with membranes that contain heterologous calcium channels or subunits thereof may be determined by using any appropriate method, such as competitive binding analysis, such as Scatchard plots, in which the binding capacity of such membranes is determined in the presence and absence of one or more concentrations of a compound having known affinity for the calcium channel. Where necessary, the results may be compared to a control experiment designed in accordance with methods known to those of skill in the art. For example, as a negative control, the results may be compared to those of assays of an identically treated membrane preparation from host cells which have not been transfected with one or more subunit-encoding nucleic acids.

The assays involve contacting the cell membrane of a recombinant eukaryotic cell which expresses at least one subunit of a human calcium channel, preferably at least an α_1 subunit of a human calcium channel, with a test compound and measuring the ability of the test compound to specifically bind to the membrane or alter or modulate the activity of a heterologous calcium channel on the membrane.

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In preferred embodiments, the assay uses a recombinant cell that has a calcium channel containing an α_1 subunit of a human calcium channel in combination with a β subunit of a human calcium channel and/or an α_2 subunit of a human calcium channel. Recombinant cells expressing heterologous calcium channels containing each of the α_1 , β and α_2 human subunits, and, optionally, a γ subunit of a human calcium channel are especially preferred for use in such assays.

In certain embodiments, the assays for identifying compounds that modulate calcium channel activity are practiced by measuring the calcium channel activity of a eukaryotic cell having a heterologous, functional calcium channel when such cell is exposed to a solution containing the test compound and a calcium channel-selective ion and comparing the measured calcium channel activity to the calcium channel activity of the same cell or a substantially identical control cell in a solution not containing the test compound. The cell is maintained in a solution having a concentration of calcium channel-selective ions sufficient to provide an inward current when the channels open. Recombinant cells expressing calcium channels that include each of the α_1 , β and α_2 human subunits, and, optionally, a γ subunit of a human calcium channel, are especially preferred for use in such assays. Methods for practicing such assays are known to those of skill in the art. For example, for similar methods applied with *Xenopus laevis* oocytes and acetylcholine receptors, see, Mishina et al. [(1985) *Nature* 313:364] and, with such oocytes and sodium channels [see, Noda et al. (1986) *Nature* 322:826-828]. For similar studies which have been carried out with the acetylcholine receptor, see, e.g., Claudio et al. [(1987) *Science* 238:1688-1694].

Functional recombinant or heterologous calcium channels may be identified by any method known to those of skill in the art. For example, electrophysiological procedures for measuring the current across an ion-selective membrane of a cell, which are well known, may be used. The amount and

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duration of the flow of calcium-selective ions through heterologous calcium channels of a recombinant cell containing DNA encoding one or more of the subunits provided herein has been measured using electrophysiological recordings using a two electrode and the whole-cell patch clamp techniques. In order to improve the sensitivity of the assays, known methods can be used to eliminate or reduce non-calcium currents and calcium currents resulting from endogenous calcium channels, when measuring calcium currents through recombinant channels.

For example, the DHP Bay K 8644 specifically enhances L-type calcium channel function by increasing the duration of the open state of the channels [see, e.g., Hess, J.B., et al. (1984) *Nature* 311:538-544]. Prolonged opening of the channels results in calcium currents of increased magnitude and duration. Tail currents can be observed upon repolarization of the cell membrane after activation of ion channels by a depolarizing voltage command. The opened channels require a finite time to close or "deactivate" upon repolarization, and the current that flows through the channels during this period is referred to as a tail current. Because Bay K 8644 prolongs opening events in calcium channels, it tends to prolong these tail currents and make them more pronounced.

In practicing these assays, stably or transiently transfected cells or injected cells that express voltage-dependent human calcium channels containing one or more of the subunits of a human calcium channel desirably may be used in assays to identify agents, such as calcium channel agonists and antagonists, that modulate calcium channel activity. Functionally testing the activity of test compounds, including compounds having unknown activity, for calcium channel agonist or antagonist activity to determine if the test compound potentiates, inhibits or otherwise alters the flow of calcium ions or other ions through a human calcium channel can be accomplished by (a) maintaining a eukaryotic cell which is transfected or injected to express a heterologous functional calcium channel capable of regulating the flow of calcium

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channel-selective ions into the cell in a medium containing calcium channel-selective ions (i) in the presence of and (ii) in the absence of a test compound; (b) maintaining the cell under conditions such that the heterologous calcium channels are substantially closed and endogenous calcium channels of the cell are substantially inhibited (c) depolarizing the membrane of the cell maintained in step (b) to an extent and for an amount of time sufficient to cause (preferably, substantially only) the heterologous calcium channels to become permeable to the calcium channel-selective ions; and (d) comparing the amount and duration of current flow into the cell in the presence of the test compound to that of the current flow into the cell, or a substantially similar cell, in the absence of the test compound.

The assays thus use cells, provided herein, that express heterologous functional calcium channels and measure functionally, such as electrophysiologically, the ability of a test compound to potentiate, antagonize or otherwise modulate the magnitude and duration of the flow of calcium channel-selective ions, such as Ca^{++} or Ba^{++} , through the heterologous functional channel. The amount of current which flows through the recombinant calcium channels of a cell may be determined directly, such as electrophysiologically, or by monitoring an independent reaction which occurs intracellularly and which is directly influenced in a calcium (or other) ion dependent manner. Any method for assessing the activity of a calcium channel may be used in conjunction with the cells and assays provided herein. For example, in one embodiment of the method for testing a compound for its ability to modulate calcium channel activity, the amount of current is measured by its modulation of a reaction which is sensitive to calcium channel-selective ions and uses a eukaryotic cell which expresses a heterologous calcium channel and also contains a transcriptional control element operatively linked for expression to a structural gene that encodes an indicator protein. The transcriptional control

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element used for transcription of the indicator gene is responsive in the cell to a calcium channel-selective ion, such as Ca^{2+} and Ba^{+} . The details of such transcriptional based assays are described in commonly owned PCT International Patent Application No. PCT/US91/5625, filed August 7, 1991, which claims priority to copending commonly owned allowed U.S. Application Serial No. 07/563,751, filed August 7, 1990; see also, commonly owned published PCT International Patent Application PCT US92/11090, which corresponds to co-pending U.S. Applications Serial Nos. 08/229,150 and 08/244,985.

Assays for diagnosis of LES

LES is an autoimmune disease characterized by an insufficient release of acetylcholine from motor nerve terminals which normally are responsive to nerve impulses. Immunoglobulins (IgG) from LES patients block individual voltage-dependent calcium channels and thus inhibit calcium channel activity [Kim and Neher, *Science* 239:405-408 (1988)]. A diagnostic assay for Lambert Eaton Syndrome (LES) is provided herein. The diagnostic assay for LES relies on the immunological reactivity of LES IgG with the human calcium channels or particular subunits alone or in combination or expressed on the surface of recombinant cells. For example, such an assay may be based on immunoprecipitation of LES IgG by the human calcium channel subunits and cells that express such subunits provided herein.

Clinical applications

In relation to therapeutic treatment of various disease states, the availability of DNA encoding human calcium channel subunits permits identification of any alterations in such genes (e.g., mutations) which may correlate with the occurrence of certain disease states. In addition, the creation of animal models of such disease states becomes possible, by specifically introducing such mutations into synthetic DNA fragments can then be introduced into laboratory animals or *in vitro* assay systems to determine the effects thereof.

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Also, genetic screening can be carried out using the nucleotide sequences as probes. Thus, nucleic acid samples from subjects having pathological conditions suspected of involving alteration/modification of any one or more of the calcium channel subunits can be screened with appropriate probes to determine if any abnormalities exist with respect to any of the endogenous calcium channels. Similarly, subjects having a family history of disease states related to calcium channel dysfunction can be screened to determine if they are also predisposed to such disease states.

EXAMPLES

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

EXAMPLE I: PREPARATION OF LIBRARIES USED FOR ISOLATION OF DNA ENCODING HUMAN NEURONAL VOLTAGE-DEPENDENT CALCIUM CHANNEL SUBUNITS

A. RNA Isolation

1. IMR32 cells

IMR32 cells were obtained from the American Type Culture Collection (ATCC Accession No. CCL127, Rockville, MD) and grown in DMEM, 10% fetal bovine serum, 1% penicillin/streptomycin (GIBCO, Grand Island, NY) plus 1.0 mM dibutyryl cAMP (dbcAMP) for ten days. Total RNA was isolated from the cells according to the procedure described by H.C. Birnboim [(1988) *Nucleic Acids Research* 16:1487-1497]. Poly(A⁺) RNA was selected according to standard procedures [see, e.g., Sambrook et al. (1989) *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory Press; pg. 7.26-7.29].

2. Human thalamus tissue

Human thalamus tissue (2.34 g), obtained from the National Neurological Research Bank, Los Angeles, CA, that had been stored frozen at -70°C was pulverized using a mortar and pestle in the presence of liquid nitrogen and the cells were lysed in 12 ml of lysis buffer (5 M guanidinium isothiocyanate, 50 mM TRIS, pH 7.4, 10 mM EDTA, 5% β -

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mercaptoethanol). Lysis buffer was added to the lysate to yield a final volume of 17 ml. N-laurylsarcosine and CsCl were added to the mixture to yield final concentrations of 4% and 0.01 g/ml, respectively, in a final volume of 18 ml.

The sample was centrifuged at 9,000 rpm in a Sorvall SS34 rotor for 10 min at room temperature to remove the insoluble material as a pellet. The supernatant was divided into two equal portions and each was layered onto a 2-ml cushion of a solution of 5.7 M CsCl, 0.1 M EDTA contained in separate centrifuge tubes to yield approximately 9 ml per tube. The samples were centrifuged in an SW41 rotor at 37,000 rpm for 24 h at 20°C.

After centrifugation, each RNA pellet was resuspended in 3 ml ETS (10 mM TRIS, pH 7.4, 10 mM EDTA, 0.2% SDS) and combined into a single tube. The RNA was precipitated with 0.25 M NaCl and two volumes of 95% ethanol.

The precipitate was collected by centrifugation and resuspended in 4 ml PK buffer (0.05 M TRIS, pH 8.4, 0.14 M NaCl, 0.01 M EDTA, 1% SDS). Proteinase K was added to the sample to a final concentration of 200 µg/ml. The sample was incubated at 22°C for 1 h, followed by extraction with an equal volume of phenol:chloroform:isoamylalcohol (50:48:2) two times, followed by one extraction with an equal volume of chloroform: isoamylalcohol (24:1). The RNA was precipitated with ethanol and NaCl. The precipitate was resuspended in 400 µl of ETS buffer. The yield of total RNA was approximately 1.0 mg. Poly A⁺ RNA (30 µg) was isolated from the total RNA according to standard methods as stated in Example I.A.1.

B. Library Construction

Double-stranded cDNA was synthesized according to standard methods [see, e.g., Sambrook et al. (1989) *IN: Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Chapter 8]. Each library was prepared in substantially the same manner except for differences in: 1) the oligonucleotide used to prime the first strand cDNA synthesis, 2) the adapters that were attached to the double-

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stranded cDNA, 3) the method used to remove the free or unused adapters, and 4) the size of the fractionated cDNA ligated into the λ phage vector.

1. IMR32 cDNA library #1

Single-stranded cDNA was synthesized using IMR32 poly(A⁺) RNA (Example I.A.1.) as a template and was primed using oligo (dT)₁₂₋₁₈ (Collaborative Research Inc., Bedford, MA): The single-stranded cDNA was converted to double-stranded cDNA and the yield was approximately 2 μ g. EcoI adapters:

5'-AATTCGGTACGTACACTCGAGC-3' = 22-mer (SEQ ID No.15)

3'-GCCATGCATGTGAGCTCG-5' = 18-mer (SEQ ID No.16)

also containing SnaBI and XhoI restriction sites were then added to the double-stranded cDNA according to the following procedure.

a. Phosphorylation of 18-mer

The 18-mer was phosphorylated using standard methods [see, e.g., Sambrook et al. (1989) IN: *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Chapter 8] by combining in a 10 μ l total volume the 18-mer (225 pmoles) with [³²P] γ -ATP (7000 Ci/mmol; 1.0 μ l) and kinase (2 U) and incubating at 37° C for 15 minutes. After incubation, 1 μ l 10 mM ATP and an additional 2 U of kinase were added and incubated at 37°C for 15 minutes. Kinase was then inactivated by boiling for 10 minutes.

b. Hybridization of 22-mer

The 22-mer was hybridized to the phosphorylated 18-mer by addition of 225 pmoles of the 22-mer (plus water to bring volume to 15 μ l), and incubation at 65°C for 5 minutes. The reaction was then allowed to slow cool to room temperature.

The adapters were thus present at a concentration of 15 pmoles/ μ l, and were ready for cDNA-adaptor ligation.

c. Ligation of adapters to cDNA

After the EcoRI, SnaBI, XhoI adapters were ligated to the double-stranded cDNA using a standard protocol [see, e.g., Sambrook et al. (1989) IN: *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Chapter 8], the

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ligase was inactivated by heating the mixture to 72°C for 15 minutes. The following reagents were added to the cDNA ligation reaction and heated at 37°C for 30 minutes: cDNA ligation reaction (20 µl), water (24 µl), 10x kinase buffer (3 µl), 10 mM ATP (1 µl) and kinase (2 µl of 2 U/µl). The reaction was stopped by the addition of 2 µl 0.5M EDTA, followed by one phenol/chloroform extraction and one chloroform extraction.

d. Size Selection and Packaging of cDNA

The double-stranded cDNA with the *EcoRI*, *SnaBI*, *XhoI* adapters ligated was purified away from the free or unligated adapters using a 5 ml Sepharose CL-4B column (Sigma, St. Louis, MO). 100 µl fractions were collected and those containing the cDNA, determined by monitoring the radioactivity, were pooled, ethanol precipitated, resuspended in TE buffer and loaded onto a 1% agarose gel. After the electrophoresis, the gel was stained with ethidium bromide and the 1 to 3 kb fraction was cut from the gel. The cDNA embedded in the agarose was eluted using the "Geneluter Electroelution System" (Invitrogen, San Diego, CA). The eluted cDNA was collected by ethanol precipitation and resuspended in TE buffer at 0.10 pmol/µl. The cDNA was ligated to 1 µg of *EcoRI* digested, dephosphorylated λgt11 in a 5 µl reaction volume at a 2- to 4- fold molar excess ratio of cDNA over the λgt11 vector. The ligated λgt11 containing the cDNA insert was packaged into λ phage virions *in vitro* using the Gigapack (Stratagene, La Jolla, CA) kit. The packaged phage were plated on an *E. coli* Y1088 bacterial lawn in preparation for screening.

2. IMR32 cDNA library #2

This library was prepared as described (Example I.B.1.) with the exception that 3 to 9 kb cDNA fragments were ligated into the λgt11 phage vector rather than the 1 to 3 kb fragments.

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3. IMR32 cDNA library #3

IMR32 cell poly(A⁺) RNA (Example I.A.1.) was used as a template to synthesize single-stranded cDNA. The primers for the first strand cDNA synthesis were random primers (hexadeoxy-nucleotides [pd(N)₆] Cat #5020-1, Clontech, Palo Alto, CA). The double-stranded cDNA was synthesized, *EcoRI*, *SnaBI*, *XhoI* adapters were added to the cDNA, the unligated adapters were removed, and the double-stranded cDNA with the ligated adapters was fractionated on an agarose gel, as described in Example I.B.1. The cDNA fraction greater than 1.8 kb was eluted from the agarose, ligated into λ gt11, packaged, and plated into a bacterial lawn of Y1088 (as described in Example I.B.1.).

4. IMR32 cDNA library #4

IMR32 cell poly(A⁺) RNA (Example I.A.1.) was used as a template to synthesize single-stranded cDNA. The primers for the first strand cDNA synthesis were oligonucleotides: 89-365a specific for the α_{1D} (VDCC III) type α_1 -subunit (see Example II.A.) coding sequence (the complementary sequence of nt 2927 to 2956, SEQ ID No. 1), 89-495 specific for the α_{1C} (VDCC II) type α_1 -subunit (see Example II.B.) coding sequence (the complementary sequence of nt 852 to 873, SEQ ID No. 3), and 90-12 specific for the α_{1C} -subunit coding sequence (the complementary sequence of nt 2496 to 2520, SEQ ID No. 3). The cDNA library was then constructed as described (Example I.B.3), except that the cDNA size-fraction greater than 1.5 kb was eluted from the agarose rather than the greater than 1.8 kb fraction.

5. IMR32 cDNA library #5

The cDNA library was constructed as described (Example I.B.3.) with the exception that the size-fraction greater than 1.2 kb was eluted from the agarose rather than the greater than 1.8 kb fraction.

6. Human thalamus cDNA library #6

Human thalamus poly (A⁺) RNA (Example I.A.2.) was used as a template to synthesize single-stranded cDNA. Oligo (dT) was

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used to prime the first strand synthesis (Example I.B.1.). The double-stranded cDNA was synthesized (Example I.B.1.) and *EcoRI*, *KpnI*, *NcoI* adapters of the following sequence:

5' CCATGGTACCTTCGTTGACG 3' = 20-mer (SEQ ID NO. 17)
3' GGTACCATGGAAGCAACTGCTTAA 5' = 24-mer (SEQ ID NO. 18)

were ligated to the double-stranded cDNA as described (Example I.B.1.) with the 20-mer replacing the 18-mer and the 24-mer replacing the 22-mer. The unligated adapters were removed by passing the cDNA-adaptor mixture through a 1 ml Bio Gel A-50 (Bio-Rad Laboratories, Richmond, CA) column. Fractions (30 μ l) were collected and 1 μ l of each fraction in the first peak of radioactivity was electrophoresed on a 1% agarose gel. After electrophoresis, the gel was dried on a vacuum gel drier and exposed to x-ray film. The fractions containing cDNA fragments greater than 600 bp were pooled, ethanol precipitated, and ligated into λ gt11 (Example I.B.1.). The construction of the cDNA library was completed as described (Example I.B.1.).

C. Hybridization and Washing Conditions

Hybridization of radiolabelled nucleic acids to immobilized DNA for the purpose of screening cDNA libraries, DNA Southern transfers, or northern transfers was routinely performed in standard hybridization conditions [hybridization: 50% deionized formamide, 200 μ g/ml sonicated herring sperm DNA (Cat #223646, Boehringer Mannheim Biochemicals, Indianapolis, IN), 5 x SSPE, 5 x Denhardt's, 42° C.; wash : 0.2 x SSPE, 0.1% SDS, 65° C]. The recipes for SSPE and Denhardt's and the preparation of deionized formamide are described, for example, in Sambrook et al. (1989) *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Chapter 8). In some hybridizations, lower stringency conditions were used in that 10% deionized formamide replaced 50% deionized formamide described for the standard hybridization conditions.

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The washing conditions for removing the non-specific probe from the filters was either high, medium, or low stringency as described below:

- 1) high stringency: 0.1 x SSPE, 0.1% SDS, 65°C
- 2) medium stringency: 0.2 x SSPE, 0.1% SDS, 50°C
- 3) low stringency: 1.0 x SSPE, 0.1% SDS, 50°C.

It is understood that equivalent stringencies may be achieved using alternative buffers, salts and temperatures.

EXAMPLE II: ISOLATION OF DNA ENCODING THE HUMAN NEURONAL CALCIUM CHANNEL α_1 SUBUNIT

A. Isolation of DNA encoding the α_{1D} subunit

1. Reference list of partial α_{1D} cDNA clones

Numerous α_{1D} -specific cDNA clones were isolated in order to characterize the complete α_{1D} coding sequence plus portions of the 5' and 3' untranslated sequences. SEQ ID No. 1 shows the complete α_{1D} DNA coding sequence, plus 510 nucleotides of α_{1D} 5' untranslated sequence ending in the guanine nucleotide adjacent to the adenine nucleotide of the proposed initiation of translation as well as 642 nucleotides of 3' untranslated sequence. Also shown in SEQ ID No. 1 is the deduced amino acid sequence. A list of partial cDNA clones used to characterize the α_{1D} sequence and the nucleotide position of each clone relative to the full-length α_{1D} cDNA sequence, which is set forth in SEQ ID No. 1, is shown below. The isolation and characterization of these clones are described below (Example II.A.2.).

IMR32	1.144	nt 1 to 510 of	SEQ ID No. 1
		5' untranslated sequence,	
		nt 511 to 2431,	SEQ ID No. 1
IMR32*	1.136	nt 1627 to 2988,	SEQ ID No. 1
		nt 1 to 104 of	SEQ ID No. 2
		additional exon,	
IMR32@	1.80	nt 2083 to 6468,	SEQ ID No. 1
IMR32*	1.36	nt 2857 to 4281,	SEQ ID No. 1
IMR32	1.163	nt 5200 to 7635,	SEQ ID No. 1

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* 5' of nt 1627, IMR32 1.136 encodes an intron and an additional exon described in Example II.A.2.d.

@ IMR32 1.80 contains two deletions, nt 2984 to 3131 and nt 5303 to 5349 (SEQ ID No. 1). The 148 nt deletion (nt 2984 to 3131) was corrected by performing a polymerase chain reaction described in Example II.A.3.b.

IMR32 1.36 contains a 132 nt deletion (nt 3081 to 3212).

2. Isolation and characterization of individual clones listed in Example II.A.1.

a. IMR32 1.36

Two million recombinants of the IMR32 cDNA library #1 (Example I.B.1.) were screened in duplicate at a density of approximately 200,000 plaques per 150 mm plate using a mixture of radiolabelled fragments of the coding region of the rabbit skeletal muscle calcium channel α_1 cDNA [for the sequence of the rabbit skeletal muscle calcium channel α_1 subunit cDNA, see, Tanabe et al. (1987). Nature 328:313-318]:

Fragment	Nucleotides
KpnI-EcoRI	-78 to 1006
EcoRI-XhoI	1006 to 2653
ApaI-ApaI	3093 to 4182
BglIII-SacI	4487 to 5310

The hybridization was performed using low stringency hybridization conditions (Example I.C.) and the filters were washed under low stringency (Example I.C.). Only one α_{1D} -specific recombinant (IMR32 1.36) of the 2×10^6 screened was identified. IMR32 1.36 was plaque purified by standard methods (J. Sambrook et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press, Chapter 8) subcloned into pGEM3 (Promega, Madison, WI) and characterized by DNA sequencing.

b. IMR32 1.80

Approximately 1×10^6 recombinants of the IMR32 cDNA library #2 (Example I.B.2.) were screened in duplicate at a

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density of approximately 100,000 plaques per 150 mm plate using the IMR32 1.36 cDNA fragment (Example II.A.1) as a probe. Standard hybridization conditions were used, and the filters were washed under high stringency (Example I.C.). Three positive plaques were identified one of which was IMR32 1.80. IMR32 1.80 was plaque purified by standard methods, restriction mapped, subcloned, and characterized by DNA sequencing.

c. IMR32 1.144

Approximately 1×10^6 recombinants of the IMR32 cDNA library #3 (Example I.B.3) were screened with the *EcoRI*-*PvuII* fragment (nt 2083 to 2518, SEQ ID No. 1) of IMR32 1.80. The hybridization was performed using standard hybridization conditions (Example I.C.) and the filters were washed under high stringency (Example I.C.). Three positive plaques were identified one of which was IMR32 1.144. IMR32 1.144 was plaque purified, restriction mapped, and the cDNA insert was subcloned into pGEM7Z (Promega, Madison, WI) and characterized by DNA sequencing. This characterization revealed that IMR32 1.144 has a series of ATG codons encoding seven possible initiating methionines (nt 511 to 531, SEQ ID No. 1). Nucleic acid amplification analysis, and DNA sequencing of cloned nucleic acid amplification analysis products encoding these seven ATG codons confirmed that this sequence is present in the α_{1D} transcript expressed in dbcAMP-induced IMR32 cells.

d. IMR32 1.136

Approximately 1×10^6 recombinants of the IMR32 cDNA library #4 (Example I.B.4) were screened with the *EcoRI*-*PvuII* fragment (nt 2083 to 2518, SEQ ID No. 1) of IMR32 1.80 (Example II.A.1.). The hybridization was performed using standard hybridization conditions (Example I.C.) and the filters were washed under high stringency (Example I.C.). Six positive plaques were identified one of which was IMR32 1.136. IMR32 1.136 was plaque purified, restriction mapped, and the cDNA insert was subcloned into a standard plasmid vector, pSP72 (Promega, Madison, WI.), and characterized by DNA

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sequencing. This characterization revealed that IMR32 1.136 encodes an incompletely spliced α_{1D} transcript. The clone contains nucleotides 1627 to 2988 of SEQ ID No. 1 preceded by an approximate 640 bp intron. This intron is then preceded by a 104 nt exon (SEQ ID No. 2) which is an alternative exon encoding the IS6 transmembrane domain [see, e.g., Tanabe et al. (1987) *Nature* 328:313-318 for a description of the IS1 to IVS6 transmembrane terminology] of the α_{1D} subunit and can replace nt 1627 to 1730, SEQ ID No. 1, to produce a completely spliced α_{1D} transcript.

e. IMR32 1.163

Approximately 1×10^6 recombinants of the IMR32 cDNA library #3 (Example I.B.3.) were screened with the *NcoI*-*XhoI* fragment of IMR32 1.80 (Example II.A.1.) containing nt 5811 to 6468 (SEQ ID No. 1). The hybridization was performed using standard hybridization conditions (Example I.C.) and the filters were washed under high stringency (Example I.C.). Three positive plaques were identified one of which was IMR32 1.163. IMR32 1.163 was plaque purified, restriction mapped, and the cDNA insert was subcloned into a standard plasmid vector, pSP72 (Promega, Madison, WI.), and characterized by DNA sequencing. This characterization revealed that IMR32 1.163 contains the α_{1D} termination codon, nt 6994 to 6996 (SEQ ID No. 1).

3. Construction of a full-length α_{1D} cDNA [pVDCCIII(A)]

α_{1D} cDNA clones IMR32 1.144, IMR32 1.136, IMR32 1.80, and IMR32 1.163 (Example II.A.2.) overlap and include the entire α_{1D} coding sequence, nt 511 to 6993 (SEQ ID No. 1), with the exception of a 148 bp deletion, nt 2984 to 3131 (SEQ ID No. 1). Portions of these partial cDNA clones were ligated to generate a full-length α_{1D} cDNA in a eukaryotic expression vector. The resulting vector was called pVDCCIII(A). The construction of pVDCCIII(A) was performed in four steps described in detail below: (1) the construction of pVDCCIII/5' using portions of IMR32 1.144, IMR32 1.136, and

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IMR32 1.80, (2) the construction of pVDCCIII/5'.3 that corrects the 148 nt deletion in the IMR32 1.80 portion of pVDCCIII/5', (3) the construction of pVDCCIII/3'.1 using portions of IMR32 1.80 and IMR32 1.163, and (4) the ligation of a portion of the pVDCCIII/5'.3 insert, the insert of pVDCCIII/3'.1, and pcDNA1 (Invitrogen, San Diego, CA) to form pVDCCIII(A). The vector pcDNA1 is a eukaryotic expression vector containing a cytomegalovirus (CMV) promoter which is a constitutive promoter recognized by mammalian host cell RNA polymerase II.

Each of the DNA fragments used in preparing the full-length construct was purified by electrophoresis through an agarose gel onto DE81 filter paper (Whatman, Clifton, NJ) and elution from the filter paper using 1.0 M NaCl, 10 mM TRIS, pH 8.0, 1 mM EDTA. The ligations typically were performed in a 10 μ l reaction volume with an equal molar ratio of insert fragment and a two-fold molar excess of the total insert relative to the vector. The amount of DNA used was normally about 50 ng to 100 ng.

a. pVDCCIII/5'

To construct pVDCCIII/5', IMR32 1.144 (Example II.A.2.c.) was digested with XhoI and EcoRI and the fragment containing the vector (pGEM7Z), α_{10} nt 1 to 510 (SEQ ID No. 1), and α_{10} nt 511 to 1732 (SEQ ID No. 1) was isolated by gel electrophoresis. The EcoRI-ApaI fragment of IMR32 1.136 (Example II.A.2.d.) nucleotides 1733 to 2671 (SEQ ID No. 1) was isolated, and the ApaI-HindIII fragment of IMR32 1.80 (Example II.A.2.b.), nucleotides 2672 to 4492 (SEQ ID No. 1) was isolated. The three DNA clones were ligated to form pVDCCIII/5' containing nt 1 to 510 (5' untranslated sequence; SEQ ID No. 1) and nt 511 to 4492 (SEQ ID No. 1).

b. pVDCCIII/5'.3

Comparison of the IMR32 1.36 and IMR32 1.80 DNA sequences revealed that these two cDNA clones differ through the α_{10} coding sequence, nucleotides 2984 to 3212. nucleic acid amplification analysis of IMR32 1.80 and dbcAMP-induced

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(1.0 mM, 10 days) IMR32 cytoplasmic RNA (isolated according to Ausubel, F.M. et al. (Eds) (1988) *Current Protocols in Molecular Biology*, John Wiley and Sons, New York) revealed that IMR32 1.80 had a 148 nt deletion, nt 2984 to 3131 (SEQ ID No. 1), and that IMR32 1.36 had a 132 nt deletion, nt 3081 to 3212. To perform the nucleic acid amplification analysis, the amplification reaction was primed with α_{1D} -specific oligonucleotides 112 (nt 2548 to 2572, SEQ ID No. 1) and 311 (the complementary sequence of nt 3928 to 3957, SEQ ID No. 1). These products were then reamplified using α_{1D} -specific oligonucleotides 310 (nt 2583 to 2608 SEQ ID No. 1) and 312 (the complementary sequence of nt 3883 to 3909). This reamplified product, which contains *AccI* and *BglII* restriction sites, was digested with *AccI* and *BglII* and the *AccI*-*BglII* fragment, nt 2765 to 3890 (SEQ ID No. 1) was cloned into *AccI*-*BglII* digested pVDCCIII/5' to replace the *AccI*-*BglII* pVDCCIII/5' fragment that had the deletion. This new construct was named pVDCCIII/5'.3. DNA sequence determination of pVDCCIII/5'.3 through the amplified region confirmed the 148 nt deletion in IMR32 1.80.

c. pVDCCIII/3'.1

To construct pVDCCIII/3'.1, the cDNA insert of IMR32 1.163 (Example II.A.2.e.) was subcloned into pBluescript II (Stratagene, La Jolla, CA) as an *XhoI* fragment. The *XhoI* sites on the cDNA fragment were furnished by the adapters used to construct the cDNA library (Example I.B.3.). The insert was oriented such that the translational orientation of the insert of IMR32 1.163 was opposite to that of the *lacZ* gene present in the plasmid, as confirmed by analysis of restriction enzyme digests of the resulting plasmid. This was done to preclude the possibility of expression of α_{1D} sequences in DH5 α cells transformed with this plasmid due to fusion with the *lacZ* gene. This plasmid was then digested with *HindIII* and *BglII* and the *HindIII* - *BglII* fragment (the *HindIII* site comes from the vector and the *BglII* site is at nt 6220, SEQ ID No. 1) was eliminated, thus deleting nt 5200 to 6220 (SEQ ID

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No. 1) of the IMR32 1.163 clone and removing this sequence from the remainder of the plasmid which contained the 3' *Bgl*III - *Xho*I fragment, nt 6221 to 7635 (SEQ ID No. 1). pVDCCIII/3'.1 was then made by splicing together the *Hind*III-PvuII fragment from IMR32 1.80 (nucleotides 4493-5296, SEQ ID No. 1), the PvuII - *Bgl*III fragment of IMR32 1.163 (nucleotides 5294 to 6220, SEQ ID No. 1) and the *Hind*III-*Bgl*III-digested pBluescript plasmid containing the 3' *Bgl*III/*Xho*I IMR32 1.163 fragment (nt 6221 to 7635, SEQ ID No. 1).

d. pVDCCIII(A): the full-length α_{10} construct

To construct pVDCCIII(A), the *Dra*I-*Hind*III fragment (5' untranslated sequence nt 330 to 510, SEQ ID No. 1 and coding sequence nt 511 to 4492, SEQ ID No. 1) of pVDCCIII/5'.3 (Example II.A.3.b.) was isolated; the *Hind*III-*Xho*I fragment of pVDCCIII/3'.1 (containing nt 4493 to 7635, SEQ ID No. 1, plus the *Xho*I site of the adapter) (Example II.A.3.c.) was isolated; and the plasmid vector, pCDNA1, was digested with *Eco*RV and *Xho*I and isolated on an agarose gel. The three DNA fragments were ligated and MC1061-P3 (Invitrogen, San Diego, CA) was transformed. Isolated clones were analyzed by restriction mapping and DNA sequencing and pVDCCIII(A) was identified which had the fragments correctly ligated together: *Dra*I-*Hind*III, *Hind*III-*Xho*I, *Xho*I-*Eco*RV with the blunt-end *Dra*I and *Eco*RV site ligating together to form the circular plasmid.

The amino-terminus of the α_{10} subunit is encoded by the seven consecutive 5' methionine codons (nt 511 to 531, SEQ ID No. 1). This 5' portion plus nt 532 to 537, encoding two lysine residues, were deleted from pVDCCIII(A) and replaced with an efficient ribosomal binding site (5'-ACCACC-3') to form pVDCCIII.RBS(A). Expression experiments in which transcripts of this construct were injected into *Xenopus laevis* oocytes did not result in an enhancement in the recombinant voltage-dependent calcium channel expression level relative to the level of expression in oocytes injected with transcripts of pVDCCIII(A).

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B. Isolation of DNA encoding the α_{1c} subunit

1. Reference List of Partial α_{1c} cDNA clones

Numerous α_{1c} -specific cDNA clones were isolated in order to characterize the α_{1c} coding sequence, the α_{1c} initiation of translation, and an alternatively spliced region of α_{1c} . SEQ ID No. 3 sets forth one α_{1c} coding sequence (α_{1c-1}) and deduced amino acid sequence; SEQ ID No. 36 sets forth another splice variant designated α_{1c-2} . SEQ ID No. 4 and No. 5 encode two possible amino terminal ends of an α_{1c} splice variant. SEQ ID No. 6 encodes an alternative exon for the IV S3 transmembrane domain. Other α_{1c} variants can be constructed by selecting the alternative amino terminal ends in place of the ends in SEQ ID No. 3 or 36 and/or inserting the alternative exon (SEQ ID No. 6) in the appropriate location, such as in SEQ ID NO. 3 in place of nucleotides 3904-3987. In addition, the 75 nucleotide sequence (nucleotides 1391-1465 in SEQ ID No. 3) can be deleted or inserted to produce an alternative α_{1c} splice variant.

Shown below is a list of clones used to characterize the α_{1c} sequence and the nucleotide position of each clone relative to the characterized α_{1c} sequence (SEQ ID No. 3). The isolation and characterization of these cDNA clones are described below (Example II.B.2).

IMR32	1.66	nt 1 to 916, SEQ ID No. 3
		nt 1 to 132, SEQ ID No. 4
IMR32	1.157	nt 1 to 873, SEQ ID No. 3
		nt 1 to 89, SEQ ID No. 5
IMR32	1.67	nt 50 to 1717, SEQ ID No. 3
*IMR32	1.86	nt 1366 to 2583, SEQ ID No. 3
*1.16G		nt 758 to 867, SEQ ID No. 3
IMR32	1.37	nt 2804 to 5904, SEQ ID No. 3
CNS	1.30	nt 2199 to 3903, SEQ ID No. 3
		nt 1 to 84 of alternative exon,
		SEQ ID No. 6
IMR32	1.38	nt 2448 to 4702, SEQ ID No. 3
		nt 1 to 84 of alternative exon,

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SEQ ID No. 6

* IMR32 1.86 has a 73 nt deletion compared to the rabbit cardiac muscle calcium channel α_1 subunit cDNA sequence.

*1.16G is an α_{1c} genomic clone.

2. Isolation and characterization of clones described in Example II.B.1.

a. CNS 1.30

Approximately 1×10^6 recombinants of the human thalamus cDNA library No. 6 (Example I.B.6.) were screened with fragments of the rabbit skeletal muscle calcium channel α_1 cDNA described in Example II.A.2.a. The hybridization was performed using standard hybridization conditions (Example I.C.) and the filters were washed under low stringency (Example I.C.). Six positive plaques were identified, one of which was CNS 1.30. CNS 1.30 was plaque purified, restriction mapped, subcloned, and characterized by DNA sequencing. CNS 1.30 encodes α_{1c} -specific sequence nt 2199 to 3903 (SEQ ID No. 3) followed by nt 1 to 84 of one of two identified alternative α_{1c} exons (SEQ ID No. 6). 3' of SEQ ID No. 6, CNS 1.30 contains an intron and, thus, CNS 1.30 encodes a partially spliced α_{1c} transcript.

b. 1.16G

Approximately 1×10^6 recombinants of a λ EMBL3-based human genomic DNA library (Cat # HL1006d Clontech Corp., Palo Alto, CA) were screened using a rabbit skeletal muscle cDNA fragment (nt -78 to 1006, Example II.A.2.a.). The hybridization was performed using standard hybridization conditions (Example I.C.) and the filters were washed under low stringency (Example I.C.). Fourteen positive plaques were identified, one of which was 1.16G. Clone 1.16G was plaque purified, restriction mapped, subcloned, and portions were characterized by DNA sequencing. DNA sequencing revealed that 1.16G encodes α_{1c} -specific sequence as described in Example II.B.1.

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c. IMR32 1.66 and IMR32 1.67

Approximately 1×10^6 recombinants of IMR32 cDNA library #5 (Example I.B.5.) were screened with a 151 bp KpnI-SacI fragment of 1.16G (Example II.B.2.b.) encoding α_{1c} sequence (nt 758 to 867, SEQ ID No. 3). The hybridization was performed using standard hybridization conditions (Example I.C.). The filters were then washed in $0.5 \times$ SSPE at 65°C . Of the positive plaques, IMR32 1.66 and IMR32 1.67 were identified. The hybridizing plaques were purified, restriction mapped, subcloned, and characterized by DNA sequencing. Two of these cDNA clones, IMR32 1.66 and 1.67, encode α_{1c} subunits as described (Example II.B.1.). In addition, IMR32 1.66 encodes a partially spliced α_{1c} transcript marked by a GT splice donor dinucleotide beginning at the nucleotide 3' of nt 916 (SEQ ID No. 3). The intron sequence within 1.66 is 101 nt long. IMR32 1.66 encodes the α_{1c} initiation of translation, nt 1 to 3 (SEQ ID No. 3) and 132 nt of 5' untranslated sequence (SEQ ID No. 4) precede the start codon in IMR32 1.66.

d. IMR32 1.37 and IMR32 1.38

Approximately 2×10^6 recombinants of IMR32 cDNA library #1 (Example I.B.1.) were screened with the CNS 1.30 cDNA fragment (Example II.B.2.a.). The hybridization was performed using low stringency hybridization conditions (Example I.C.) and the filters were washed under low stringency (Example I.C.). Four positive plaques were identified, plaque purified, restriction mapped, subcloned, and characterized by DNA sequencing. Two of the clones, IMR32 1.37 and IMR32 1.38 encode α_{1c} -specific sequences as described in Example II.B.1.

DNA sequence comparison of IMR32 1.37 and IMR32 1.38 revealed that the α_{1c} transcript includes two exons that encode the IVS3 transmembrane domain. IMR32 1.37 has a single exon, nt 3904 to 3987 (SEQ ID No. 3) and IMR32 1.38 appears to be anomalously spliced to contain both exons juxtaposed, nt 3904 to 3987 (SEQ ID No. 3) followed by nt 1 to 84 (SEQ ID No. 6). The alternative splice of the α_{1c} transcript to contain either of the two exons encoding the IVS3 region was confirmed by

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comparing the CNS 1.30 sequence to the IMR32 1.37 sequence. CNS 1.30 contains nt 1 to 84 (SEQ ID No. 6) preceded by the identical sequence contained in IMR32 1.37 for nt 2199 to 3903 (SEQ ID No. 3). As described in Example II.B.2.a., an intron follows nt 1 to 84 (SEQ ID No. 6). Two alternative exons have been spliced adjacent to nt 3903 (SEQ ID No. 3) represented by CNS 1.30 and IMR32 1.37.

e. IMR32 1.86

IMR32 cDNA library #1 (Example I.B.1.) was screened in duplicate using oligonucleotide probes 90-9 (nt 1462 to 1491, SEQ ID No. 3) and 90-12 (nt 2496 to 2520, SEQ ID No. 3). These oligonucleotide probes were chosen in order to isolate a clone that encodes the α_{1c} subunit between the 3' end of IMR32 1.67 (nt 1717, SEQ ID No. 3) and the 5' end of CNS 1.30 (nt 2199, SEQ ID No. 3). The hybridization conditions were standard hybridization conditions (Example I.C.) with the exception that the 50% deionized formamide was reduced to 20%. The filters were washed under low stringency (Example I.C.). Three positive plaques were identified one of which was IMR32 1.86. IMR32 1.86 was plaque purified, subcloned, and characterized by restriction mapping and DNA sequencing. IMR32 1.86 encodes α_{1c} sequences as described in Example II.B.1. Characterization by DNA sequencing revealed that IMR32 1.86 contains a 73 nt deletion compared to the DNA encoding rabbit cardiac muscle calcium channel α_1 subunit [Mikami et al. (1989) Nature 340:230], nt 2191 to 2263. These missing nucleotides correspond to nt 2176-2248 of SEQ ID No. 3. Because the 5'-end of CNS 1.30 overlaps the 3'-end of IMR32 1.86, some of these missing nucleotides, i.e., nt 2205-2248 of SEQ ID No. 3, are accounted for by CNS 1.30. The remaining missing nucleotides of the 73 nucleotide deletion in IMR32 1.86 (i.e., nt 2176-2204 SEQ ID No. 3) were determined by nucleic acid amplification analysis of dbcAMP-induced IMR32 cell RNA. The 73 nt deletion is a frame-shift mutation and, thus, needs to be corrected. The exact human sequence through this region, (which has been determined by the DNA sequence of

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CNS 1.30 and nucleic acid amplification analysis of IMR32 cell RNA) can be inserted into IMR32 1.86 by standard methods, e.g., replacement of a restriction fragment or site-directed mutagenesis.

f. IMR32 1.157

One million recombinants of IMR32 cDNA library #4 (Example I.B.4.) were screened with an *Xho*I-*Eco*RI fragment of IMR32 1.67 encoding α_{1c} nt 50 to 774 (SEQ ID No. 3). The hybridization was performed using standard hybridization conditions (Example I.C.). The filters were washed under high stringency (Example I.C.). One of the positive plaques identified was IMR32 1.157. This plaque was purified, the insert was restriction mapped and subcloned to a standard plasmid vector pGEM7Z (Promega, Madison, WI). The DNA was characterized by sequencing. IMR32 1.157 appears to encode an alternative 5' portion of the α_{1c} sequence beginning with nt 1 to 89 (SEQ ID No. 5) and followed by nt 1 to 873 (SEQ ID No. 3). Analysis of the 1.66 and 1.157 5' sequence is described below (Example II.B.3.).

3. Characterization of the α_{1c} initiation f translation site

Portions of the sequences of IMR32 1.157 (nt 57 to 89, SEQ ID No. 5; nt 1 to 67, SEQ ID No. 3), IMR32 1.66 (nt 100 to 132, SEQ ID No. 4; nt 1 to 67, SEQ ID No. 3), were compared to the rabbit lung CaCB-receptor cDNA sequence, nt -33 to 67 [Biel et al. (1990) *FEBS Lett.* 269:409]. The human sequences are possible alternative 5' ends of the α_{1c} transcript encoding the region of initiation of translation. IMR32 1.66 closely matches the CaCB receptor cDNA sequence and diverges from the CaCB receptor cDNA sequence in the 5' direction beginning at nt 122 (SEQ ID No. 4). The start codon identified in the CaCB receptor cDNA sequence is the same start codon used to describe the α_{1c} coding sequence, nt 1 to 3 (SEQ ID No. 3).

The sequences of α_{1c} splice variants, designated α_{1c-1} and α_{1c-2} are set forth in SEQ ID NOS. 3 and 36.

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C. Isolation of partial cDNA clones encoding the α_{1B} subunit and construction of a full-length clone

A human basal ganglia cDNA library was screened with the rabbit skeletal muscle α_1 subunit cDNA fragments (see Example II.A.2.a for description of fragments) under low stringency conditions. One of the hybridizing clones was used to screen an IMR32 cell cDNA library to obtain additional partial α_{1B} cDNA clones, which were in turn used to further screen an IMR32 cell cDNA library for additional partial cDNA clones. One of the partial IMR32 α_{1B} clones was used to screen a human hippocampus library to obtain a partial α_{1B} clone encoding the 3' end of the α_{1B} coding sequence. The sequence of some of the regions of the partial cDNA clones was compared to the sequence of products of nucleic acid amplification analysis of IMR32 cell RNA to determine the accuracy of the cDNA sequences.

Nucleic acid amplification analysis analysis of IMR32 cell RNA and genomic DNA using oligonucleotide primers corresponding to sequences located 5' and 3' of the STOP codon of the DNA encoding the α_{1B} subunit revealed an alternatively spliced α_{1B} -encoding mRNA in IMR32 cells. This second mRNA product is the result of differential splicing of the α_{1B} subunit transcript to include another exon that is not present in the mRNA corresponding to the other 3' α_{1B} cDNA sequence that was initially isolated. To distinguish these splice variants of the α_{1B} subunit, the subunit encoded by a DNA sequence corresponding to the form containing the additional exon is referred to as α_{1B-1} (SEQ ID No. 7), whereas the subunit encoded by a DNA sequence corresponding to the form lacking the additional exon is referred to as α_{1B-2} (SEQ ID No. 8). The sequence of α_{1B-1} diverges from that of α_{1B-2} beginning at nt 6633 (SEQ ID No. 7). Following the sequence of the additional exon in α_{1B-1} (nt 6633-6819; SEQ ID No. 7), the α_{1B-1} and α_{1B-2} sequences are identical (i.e., nt 6820-7362 in SEQ ID No. 7 and nt 6633-7175 in SEQ ID No. 8). SEQ ID No. 7 and No. 8 set forth 143 nt of 5' untranslated sequence (nt 1-143) as well as

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202 nt of 3' untranslated sequence (nt 7161-7362, SEQ ID No. 7) of the DNA encoding α_{1B-1} and 321 nt of 3' untranslated sequence (nt 6855-7175, SEQ ID No. 8) of the DNA encoding α_{1B-2} .

Nucleic acid amplification analysis analysis of the IS6 region of the α_{1B} transcript revealed what appear to be additional splice variants based on multiple fragment sizes seen on an ethidium bromide-stained agarose gel containing the products of the amplification reaction.

A full-length α_{1B-1} cDNA clone designated pcDNA- α_{1B-1} was prepared in an eight-step process as follows.

- STEP 1: The *SacI* restriction site of pGEM3 (Promega, Madison, WI) was destroyed by digestion at the *SacI* site, producing blunt ends by treatment with T4 DNA polymerase, and religation. The new vector was designated pGEMASac.
- STEP 2: Fragment 1 (*HindIII*/*KpnI*; nt 2337 to 4303 of SEQ ID No. 7) was ligated into *HindIII*/*KpnI* digested pGEM3ASac to produce p α 1.177HK.
- STEP 3: Fragment 1 has a 2 nucleotide deletion (nt 3852 and 3853 of SEQ ID No. 7). The deletion was repaired by inserting an amplified fragment (fragment 2) of IMR32 RNA into p α 1.177HK. Thus, fragment 2 (*NarI*/*KpnI*; nt 3828 to 4303 of SEQ ID No. 7) was inserted into *NarI*/*KpnI* digested p α 1.177HK replacing the *NarI*/*KpnI* portion of fragment 1 and producing p α 1.177HK/PCR.
- STEP 4: Fragment 3 (*KpnI*/*KpnI*; nt 4303 to 5663 of SEQ ID No. 7) was ligated into *KpnI* digested p α 1.177HK/PCR to produce p α 1B5'K.
- STEP 5: Fragment 4 (*EcoRI*/*HindIII*; *EcoRI* adaptor plus nt 1 to 2337 of SEQ ID No. 7) and fragment 5 (*HindIII*/*XhoI* fragment of p α 1B5'K; nt 2337 to 5446 of SEQ ID No. 7) were ligated together into *EcoRI*/*XhoI* digested pcDNA1 (Invitrogen, San Diego, CA) to produce p α 1B5'.

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- STEP 6: Fragment 6 (*EcoRI/EcoRI*; *EcoRI* adapters on both ends plus nt 5749 to 7362 of SEQ ID No. 7) was ligated into *EcoRI* digested pBluescript II KS (Stratagene, La Jolla, CA) with the 5' end of the fragment proximal to the *KpnI* site in the polylinker to produce p α 1.230.
- STEP 7: Fragment 7 (*KpnI/XhoI*; nt 4303 to 5446 of SEQ ID No. 7), and fragment 8 (*XhoI/CspI*; nt 5446 to 6259 of SEQ ID No. 7) were ligated into *KpnI/CspI* digested p α 1.230 (removes nt 5749 to 6259 of SEQ ID No. 7 that was encoded in p α 1.230 and maintains nt 6259 to 7362 of SEQ ID No. 7) to produce p α 1B3'.
- STEP 8: Fragment 9 (*SphI/XhoI*; nt 4993 to 5446 of SEQ ID No. 7) and fragment 10 (*XhoI/XbaI* of p α 1B3'; nt 5446 to 7319 of SEQ ID No. 7) were ligated into *SphI/XbaI* digested p α 1B5' (removes nt 4993 to 5446 of SEQ ID No. 7 that were encoded in p α 1B5' and maintains nt 1 to 4850 of SEQ ID No. 7) to produce pCDNA α_{1B-1} .

The resulting construct, pCDNA α_{1B-1} , contains, in pCDNA1, a full-length coding region encoding α_{1B-1} (nt 144-7362, SEQ ID No. 7), plus 5' untranslated sequence (nt 1-143, SEQ ID No. 7) and 3' untranslated sequence (nt 7161-7319, SEQ ID No. 7) under the transcriptional control of the CMV promoter.

D. Isolation of DNA encoding human calcium channel α_{1A} subunits

1. Isolation of partial clones

DNA clones encoding portions of human calcium channel α_{1A} subunits were obtained by hybridization screening of human cerebellum cDNA libraries and nucleic acid amplification of human cerebellum RNA. Clones corresponding to the 3' end of the α_{1A} coding sequence were isolated by screening 1×10^6 recombinants of a randomly primed cerebellum cDNA library (size-selected for inserts greater than 2.8 kb in length) under low stringency conditions (6X SSPE, 5X Denhart's solution, 0.2% SDS, 200 μ g/ml sonicated herring sperm DNA,

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42°C) with oligonucleotide 704 containing nt 6190-6217 of the rat α_{1A} coding sequence [Starr et al. (1992) *Proc. Natl. Acad. Sci. U.S.A.* 88:5621-5625]. Washes were performed under low stringency conditions. Several clones that hybridized to the probe (clones $\alpha 1.251$ - $\alpha 1.259$ and $\alpha 1.244$) were purified and characterized by restriction enzyme mapping and DNA sequence analysis. At least two of the clones, $\alpha 1.244$ and $\alpha 1.254$, contained a translation termination codon. Although clones $\alpha 1.244$ and $\alpha 1.254$ are different lengths, they both contain a sequence of nucleotides that corresponds to the extreme 3' end of the α_{1A} transcript, *i.e.*, the two clones overlap. These two clones are identical in the region of overlap, except, clone $\alpha 1.244$ contains a sequence of 5 and a sequence of 12 nucleotides that are not present in $\alpha 1.254$.

To obtain additional α_{1A} -encoding clones, 1×10^6 recombinants of a randomly primed cerebellum cDNA library (size-selected for inserts ranging from 1.0 to 2.8 kb in length) was screened for hybridization to three oligonucleotides: oligonucleotide 701 (containing nucleotides 2288-2315 of the rat α_{1A} coding sequence), oligonucleotide 702 (containing nucleotides 3559-3585 of the rat α_{1A} coding sequence) and oligonucleotide 703 (containing nucleotides 4798-4827 of the rat α_{1A} coding sequence). Hybridization and washes were performed using the same conditions as used for the first screening with oligonucleotide 704, except that washes were conducted at 45°C. Twenty clones (clones $\alpha 1.269$ - $\alpha 1.288$) hybridized to the probe. Several clones were plaque-purified and characterized by restriction enzyme mapping and DNA sequence analysis. One clone, $\alpha 1.279$, contained a sequence of about 170 nucleotides that is not present in other clones corresponding to the same region of the coding sequence. This region may be present in other splice variants. None of the clones contained a translation initiation codon.

To obtain clones corresponding to the 5' end of the human α_{1A} coding sequence, another cerebellum cDNA library was

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prepared using oligonucleotide 720 (containing nucleotides 2485-2510 of SEQ ID No. 22) to specifically prime first-strand cDNA synthesis. The library (8×10^5 recombinants) was screened for hybridization to three oligonucleotides: oligonucleotide 701, oligonucleotide 726 (containing nucleotides 2333-2360 of the rat α_{1A} coding sequence) and oligonucleotide 700 (containing nucleotides 767-796 of the rat α_{1A} coding sequence) under low stringency hybridization and washing conditions. Approximately 50 plaques hybridized to the probe. Hybridizing clones $\alpha 1.381$ - $\alpha 1.390$ were plaque-purified and characterized by restriction enzyme mapping and DNA sequence analysis. At least one of the clones, $\alpha 1.381$, contained a translation initiation codon.

Alignment of the sequences of the purified clones revealed that the sequences overlapped to comprise the entire α_{1A} coding sequence. However, not all the overlapping sequences of partial clones contained convenient enzyme restriction sites for use in ligating partial clones to construct a full-length α_{1A} coding sequence. To obtain DNA fragments containing convenient restriction enzyme sites that could be used in constructing a full-length α_{1A} DNA, cDNA was synthesized from RNA isolated from human cerebellum tissue and subjected to nucleic acid amplification. The oligonucleotides used as primers corresponded to human α_{1A} coding sequence located 5' and 3' of selected restriction enzyme sites. Thus, in the first amplification reaction, oligonucleotides 753 (containing nucleotides 2368-2391 of SEQ ID No. 22) and 728 (containing nucleotides 3179-3202 of SEQ ID No. 22) were used as the primer pair. To provide a sufficient amount of the desired DNA fragment, the product of this amplification was reamplified using oligonucleotides 753 and 754 (containing nucleotides 3112-3135 of SEQ ID No. 22 as the primer pair. The resulting product was 768 bp in length. In the second amplification reaction, oligonucleotides 719 (containing nucleotides 4950-4975 of SEQ ID No. 22 and 752 (containing nucleotides 5647-5670 of SEQ ID No. 22) were used as the

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primer pair. To provide a sufficient amount of the desired second DNA fragment, the product of this amplification was reamplified using oligonucleotides 756 (containing nucleotides 5112-5135 of SEQ ID No. 22) and 752 as the primer pair. The resulting product was 559 bp in length.

2. Construction of full-length α_{1A} coding sequences

Portions of clone $\alpha 1.381$, the 768-bp nucleic acid amplification product, clone $\alpha 1.278$, the 559-bp nucleic acid amplification product, and clone $\alpha 1.244$ were ligated at convenient restriction sites to generate a full-length α_{1A} coding sequence referred to as α_{1A-1} .

Comparison of the results of sequence analysis of clones $\alpha 1.244$ and $\alpha 1.254$ indicated that the primary transcript of the α_{1A} subunit gene is alternatively spliced to yield at least two variant mRNAs encoding different forms of the α_{1A} subunit. One form, α_{1A-1} , is encoded by the sequence shown in SEQ ID No. 22. The sequence encoding a second form, α_{1A-2} , differs from the α_{1A-1} -encoding sequence at the 3' end in that it lacks a 5-nt sequence found in clone $\alpha 1.244$ (nucleotides 7035-7039 of SEQ ID No. 22). This deletion shifts the reading frame and introduces a translation termination codon resulting in an α_{1A-2} coding sequence that encodes a shorter α_{1A} subunit than that encoded by the α_{1A-1} splice variant. Consequently, a portion of the 3' end of the α_{1A-1} coding sequence is actually 3' untranslated sequence in the α_{1A-2} DNA. The complete sequence of α_{1A-2} , which can be constructed by ligating portions of clone $\alpha 1.381$, the 768-bp nucleic acid amplification product, clone $\alpha 1.278$, the 559-bp nucleic acid amplification product and clone $\alpha 1.254$, is set forth in SEQ ID No. 23.

E. Isolation of DNA Encoding the α_{1E} Subunit

DNA encoding α_{1E} subunits of the human calcium channel were isolated from human hippocampus libraries. The selected clones sequenced. DNA sequence analysis of DNA clones encoding the α_{1E} subunit indicated that at least two alternatively spliced forms of the same α_{1E} subunit primary transcript are expressed. One form has the sequence set forth

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in SEQ ID No. 24 and was designated α_{1E-1} and the other was designated α_{1E-3} , which has the sequence obtained by inserting a 57 base pair fragment between nucleotides 2405 and 2406 of SEQ ID No. 24. The resulting sequence is set forth in SEQ ID No. 25.

The subunit designated α_{1E-1} has a calculated molecular weight of 254,836 and the subunit designated α_{1E-3} has a calculated molecular weight of 257,348. α_{1E-3} has a 19 amino acid insertion (encoded by SEQ ID No. 25) relative to α_{1E-1} in the region that appears to be the cytoplasmic loop between transmembrane domains IIS6 and IIIS1.

EXAMPLE III: ISOLATION OF cDNA CLONES ENCODING THE HUMAN NEURONAL CALCIUM CHANNEL β_1 subunit

A. Isolation of partial cDNA clones encoding the β subunit and construction of a full-length clone encoding the β_1 subunit

A human hippocampus cDNA library was screened with the rabbit skeletal muscle calcium channel β_1 subunit cDNA fragment (nt 441 to 1379) [for isolation and sequence of the rabbit skeletal muscle calcium channel β_1 subunit cDNA, see U.S. Patent Application Serial NO. 482,384 or Ruth et al. (1989) *Science* 245:1115] using standard hybridization conditions (Example I.C.). A portion of one of the hybridizing clones was used to rescreen the hippocampus library to obtain additional cDNA clones. The cDNA inserts of hybridizing clones were characterized by restriction mapping and DNA sequencing and compared to the rabbit skeletal muscle calcium channel β_1 subunit cDNA sequence.

Portions of the partial β_1 subunit cDNA clones were ligated to generate a full-length clone encoding the entire β_1 subunit. SEQ ID No. 9 shows the β_1 subunit coding sequence (nt 1-1434) as well as a portion of the 3' untranslated sequence (nt 1435-1546). The deduced amino acid sequence is also provided in SEQ ID No. 9. In order to perform expression experiments, full-length β_1 subunit cDNA clones were constructed as follows.

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Step 1: DNA fragment 1 (~800 bp of 5' untranslated sequence plus nt 1-277 of SEQ ID No. 9) was ligated to DNA fragment 2 (nt 277-1546 of SEQ ID No. 9 plus 448 bp of intron sequence) and cloned into pGEM7Z. The resulting plasmid, p β 1-1.18, contained a full-length β_1 subunit clone that included a 448-bp intron.

Step 2: To replace the 5' untranslated sequence of p β 1-1.18 with a ribosome binding site, a double-stranded adapter was synthesized that contains an *EcoRI* site, sequence encoding a ribosome binding site (5'-ACCACC-3') and nt 1-25 of SEQ ID No. 9. The adapter was ligated to *SmaI*-digested p β 1-1.18, and the products of the ligation reaction were digested with *EcoRI*.

Step 3: The *EcoRI* fragment from step 2 containing the *EcoRI* adapter, efficient ribosome binding site and nt 1-1546 of SEQ ID No. 9 plus intron sequence was cloned into a plasmid vector and designated p β 1-1.18RBS. The *EcoRI* fragment of p β 1-1.18RBS was subcloned into *EcoRI*-digested pcDNA1 with the initiation codon proximal to CMV promoter to form pHBCaCH $\beta_{1,18}$ RBS(A).

Step 4: To generate a full-length clone encoding the β_1 subunit lacking intron sequence, DNA fragment 3 (nt 69-1146 of SEQ ID No. 9 plus 448 bp of intron sequence followed by nt 1147-1546 of SEQ ID No. 9), was subjected to site-directed mutagenesis to delete the intron sequence, thereby yielding p β 1(-). The *EcoRI*-*XhoI* fragment of p β 1-1.18RBS (containing of the ribosome binding site and nt 1-277 of SEQ ID No. 9) was ligated to the *XhoI*-*EcoRI* fragment of p β 1(-) (containing of nt 277-1546 of SEQ ID No. 9) and cloned into pcDNA1 with the initiation of translation proximal to the CMV promoter. The resulting expression plasmid was designated pHBCaCH $\beta_{1,18}$ RBS(A).

B. Splice Variant $\beta_{1,3}$

DNA sequence analysis of the DNA clones encoding the β_1 subunit indicated that in the CNS at least two alternatively spliced forms of the same human β_1 subunit primary transcript are expressed. One form is represented by the sequence shown

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in SEQ ID No. 9 and is referred to as $\beta_{1,2}$. The sequences of $\beta_{1,2}$ and the alternative form, $\beta_{1,3}$, diverge at nt 1334 (SEQ ID No. 9). The complete $\beta_{1,3}$ sequence (nt 1-1851), including 3' untranslated sequence (nt 1795-1851), is set forth in SEQ ID No. 10.

EXAMPLE IV: ISOLATION OF cDNA CLONES ENCODING THE HUMAN NEURONAL CALCIUM CHANNEL α_2 -subunit

A. Isolation of cDNA clones

The complete human neuronal α_2 coding sequence (nt 35-3310) plus a portion of the 5' untranslated sequence (nt 1 to 34) as well as a portion of the 3' untranslated sequence (nt 3311-3600) is set forth in SEQ ID No. 11.

To isolate DNA encoding the human neuronal α_2 subunit, human α_2 genomic clones first were isolated by probing human genomic Southern blots using a rabbit skeletal muscle calcium channel α_2 subunit cDNA fragment [nt 43 to 272, Ellis et al. (1988) *Science* 240:1661]. Human genomic DNA was digested with *EcoRI*, electrophoresed, blotted, and probed with the rabbit skeletal muscle probe using standard hybridization conditions (Example I.C.) and low stringency washing conditions (Example I.C.). Two restriction fragments were identified, 3.5 kb and 3.0 kb. These *EcoRI* restriction fragments were cloned by preparing a λ gt11 library containing human genomic *EcoRI* fragments ranging from 2.2 kb to 4.3 kb. The library was screened as described above using the rabbit α_2 probe, hybridizing clones were isolated and characterized by DNA sequencing. HGCaCH α_2 .20 contained the 3.5 kb fragment and HGCaCH α_2 .9 contained the 3.0 kb fragment.

Restriction mapping and DNA sequencing revealed that HGCaCH α_2 .20 contains an 82 bp exon (nt 130 to 211 of the human α_2 coding sequence, SEQ ID No. 11) on a 650 bp *PstI*-*XbaI* restriction fragment and that HGCaCH α_2 .9 contains 105 bp of an exon (nt 212 to 316 of the coding sequence, SEQ ID No. 11) on a 750 bp *XbaI*-*BglIII* restriction fragment. These restriction fragments were used to screen the human basal ganglia cDNA library (Example II.C.2.a.). HBCaCH α_2 .1 was isolated (nt 29

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to 1163, SEQ ID No. 11) and used to screen a human brain stem cDNA library (ATCC Accession No. 37432) obtained from the American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD. 20852. Two clones were isolated, HBCaCH α 2.5 (nt 1 to 1162, SEQ ID No. 11) and HBCaCH α 2.8 (nt 714 to 1562, SEQ ID No. 11, followed by 1600 nt of intervening sequence). A 2400 bp fragment of HBCaCH α 2.8 (beginning at nt 759 of SEQ ID No. 11 and ending at a *Sma*I site in the intron) was used to rescreen the brain stem library and to isolate HBCaCH α 2.11 (nt 879 to 3600, SEQ ID No. 11). Clones HBCaCH α 2.5 and HBCaCH α 2.11 overlap to encode an entire human brain α_2 protein.

B. Construction of pHBCaCH α_2 A

To construct pHBCaCH α_2 A containing DNA encoding a full-length human calcium channel α_2 subunit, an (*Eco*RI)-*Pvu*II fragment of HBCaCH α 2.5 (nt 1 to 1061, SEQ ID No. 11, *Eco*RI adapter, *Pvu*II partial digest) and a *Pvu*II-*Pst*I fragment of HBCaCH α 2.11 (nt 1061 to 2424 SEQ ID No. 11; *Pvu*II partial digest) were ligated into *Eco*RI-*Pst*I-digested pIBI24 (Stratagene, La Jolla, CA). Subsequently, an (*Eco*RI)-*Pst*I fragment (nt 1 to 2424 SEQ ID No. 11) was isolated and ligated to a *Pst*I-(*Eco*RI) fragment (nt 2424 to 3600 SEQ ID No. 11) of HBCaCH α 2.11 in *Eco*RI-digested pIBI24 to produce DNA, HBCaCH α 2, encoding a full-length human brain α_2 subunit. The 3600 bp *Eco*RI insert of HBCaCH α 2 (nt 1 to 3600, SEQ ID No. 11) was subcloned into pcDNA1 (pHBCaCH α 2A) with the methionine initiating codon proximal to the CMV promoter. The 3600 bp *Eco*RI insert of HBCaCH α 2 was also subcloned into pSV2dhFR [Subramani et al. (1981). *Mol. Cell. Biol.* 1:854-864] which contains the SV40 early promoter, mouse dihydrofolate reductase (*dhfr*) gene, SV40 polyadenylation and splice sites and sequences required for maintenance of the vector in bacteria.

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EXAMPLE V. DIFFERENTIAL PROCESSING OF THE HUMAN β_1 TRANSCRIPT AND THE HUMAN α_2 TRANSCRIPT

A. Differential processing of the β_1 transcript

Nucleic acid amplification analysis of the human β_1 transcript present in skeletal muscle, aorta, hippocampus and basal ganglia, and HEK 293 cells revealed differential processing of the region corresponding to nt 615-781 of SEQ ID No. 9 in each of the tissues. Four different sequences that result in five different processed β_1 transcripts through this region were identified. The β_1 transcripts from the different tissues contained different combinations of the four sequences, except for one of the β_1 transcripts expressed in HEK 293 cells ($\beta_{1,5}$) which lacked all four sequences.

None of the β_1 transcripts contained each of the four sequences; however, for ease of reference, all four sequences are set forth end-to-end as a single long sequence in SEQ ID No. 12. The four sequences that are differentially processed are sequence 1 (nt 14-34 in SEQ ID No. 12), sequence 2 (nt 35-55 in SEQ ID No. 12), sequence 3 (nt 56-190 in SEQ ID No. 12) and sequence 4 (nt 191-271 in SEQ ID No. 12). The forms of the β_1 transcript that have been identified include: (1) a form that lacks sequence 1 called $\beta_{1,1}$ (expressed in skeletal muscle), (2) a form that lacks sequences 2 and 3 called $\beta_{1,2}$ (expressed in CNS), (3) a form that lacks sequences 1, 2 and 3 called $\beta_{1,4}$ (expressed in aorta and HEK cells) and (4) a form that lacks sequences 1-4 called $\beta_{1,5}$ (expressed in HEK cells). Additionally, the $\beta_{1,4}$ and $\beta_{1,5}$ contain a guanine nucleotide (nt 13 in SEQ ID No. 12) that is absent in the $\beta_{1,1}$ and $\beta_{1,2}$ forms. The sequences of β_1 splice variants are set forth in SEQ ID Nos. 9, 10 and 33-35.

B. Differential processing of transcripts encoding the α_2 subunit.

The complete human neuronal α_2 coding sequence (nt 35-3307) plus a portion of the 5' untranslated sequence (nt 1 to 34) as well as a portion of the 3' untranslated sequence (nt 3308-3600) is set forth as SEQ ID No. 11.

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Nucleic acid amplification analysis of the human α_2 transcript present in skeletal muscle, aorta, and CNS revealed differential processing of the region corresponding to nt 1595-1942 of SEQ ID No. 11 in each of the tissues.

The analysis indicated that the primary transcript of the genomic DNA that includes the nucleotides corresponding to nt 1595-1942 also includes an additional sequence (SEQ ID No. 13: 5' CCTATTGGTGTAGGTATACCAACAATTAATTT AAGAAAAAGGAGACCCAATATCCAG 3') inserted between nt 1624 and 1625 of SEQ ID No. 11. Five alternatively spliced variant transcripts that differ in the presence or absence of one to three different portions of the region of the primary transcript that includes the region of nt 1595-1942 of SEQ ID No. 11 plus SEQ ID No. 13 inserted between nt 1624 and 1625 have been identified. The five α_2 -encoding transcripts from the different tissues include different combinations of the three sequences, except for one of the α_2 transcripts expressed in aorta which lacks all three sequences. None of the α_2 transcripts contained each of the three sequences. The sequences of the three regions that are differentially processed are sequence 1 (SEQ ID No. 13), sequence 2 (5' AACCCCAAATCTCAG 3', which is nt 1625-1639 of SEQ ID No. 11), and sequence 3 (5' CAAAAAAGGGCAAAATGAAGG 3', which is nt 1908-1928 of SEQ ID No. 11). The five α_2 forms identified are (1) a form that lacks sequence 3 called α_{2a} (expressed in skeletal muscle), (2) a form that lacks sequence 1 called α_{2b} (expressed in CNS), (3) a form that lacks sequences 1 and 2 called α_{2c} (expressed in aorta), (4) a form that lacks sequences 1, 2 and 3 called α_{2d} (expressed in aorta) and (5) a form that lacks sequences 1 and 3 called α_{2e} (expressed in aorta).

The sequences of α_{2a} - α_{2e} are set forth in SEQ. ID Nos. 29 - 32, respectively.

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EXAMPLE VI: ISOLATION OF DNA ENCODING A CALCIUM CHANNEL γ SUBUNIT FROM A HUMAN BRAIN cDNA LIBRARY**A. Isolation of DNA encoding the γ subunit**

Approximately 1×10^6 recombinants from a λ gt11-based human hippocampus cDNA library (Clontech catalog #HL1088b, Palo Alto, CA) were screened by hybridization to a 484 bp sequence of the rabbit skeletal muscle calcium channel γ subunit cDNA (nucleotides 621-626 of the coding sequence plus 438 nucleotides of 3'-untranslated sequence) contained in vector γ J10 [Jay, S. et al. (1990). *Science* 248:490-492]. Hybridization was performed using moderate stringency conditions (20% deionized formamide, 5x Denhardt's, 6 x SSPE, 0.2% SDS, 20 μ g/ml herring sperm DNA, 42°C) and the filters were washed under low stringency (see Example I.C.). A plaque that hybridized to this probe was purified and insert DNA was subcloned into pGEM7Z. This cDNA insert was designated γ 1.4.

B. Characterization of γ 1.4

γ 1.4 was confirmed by DNA hybridization and characterized by DNA sequencing. The 1500 bp *Sst*I fragment of γ 1.4 hybridized to the rabbit skeletal muscle calcium channel γ subunit cDNA γ J10 on a Southern blot. SEQ analysis of this fragment revealed that it contains of approximately 500 nt of human DNA sequence and ~1000 nt of λ gt11 sequence (included due to apparent destruction of one of the *Eco*RI cloning sites in λ gt11). The human DNA sequence contains of 129 nt of coding sequence followed immediately by a translational STOP codon and 3' untranslated sequence (SEQ ID No. 14).

To isolate the remaining 5' sequence of the human γ subunit cDNA, human CNS cDNA libraries and/or preparations of mRNA from human CNS tissues can first be assayed by nucleic acid amplification analysis methods using oligonucleotide primers based on the γ cDNA-specific sequence of γ 1.4. Additional human neuronal γ subunit-encoding DNA can be isolated from cDNA libraries that, based on the results of the nucleic acid amplification analysis assay, contain γ -specific

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amplifiable cDNA. Alternatively, cDNA libraries can be constructed from mRNA preparations that, based on the results of the nucleic acid amplification analysis assays, contain γ -specific amplifiable transcripts. Such libraries are constructed by standard methods using oligo dT to prime first-strand cDNA synthesis from poly A⁺ RNA (see Example I.B.). Alternatively, first-strand cDNA can be specified by priming first-strand cDNA synthesis with a γ cDNA-specific oligonucleotide based on the human DNA sequence in γ 1.4. A cDNA library can then be constructed based on this first-strand synthesis and screened with the γ -specific portion of γ 1.4.

EXAMPLE VII: ISOLATION OF cDNA CLONES ENCODING THE HUMAN NEURONAL Ca CHANNEL β_2 SUBUNIT

Isolation of DNA Encoding human calcium channel β_2 subunits

Sequencing of clones isolated as described in Example III revealed a clone encoding a human neuronal calcium channel β_2 subunit (designated β_{2D} see, SEQ ID No. 26). An oligonucleotide based on the 5' end of this clone was used to prime a human hippocampus cDNA library. The library was screened with this β_2 clone under conditions of low to medium stringency (final wash 0.5 X SSPE, 50° C). Several hybridizing clones were isolated and sequenced. Among these clones were those that encode β_{2C} , β_{2D} and β_{2E} . For example, the sequence of β_{2C} is set forth in SEQ ID NO. 37, and the sequence of β_{2E} is set forth in SEQ ID No. 38.

A randomly primed hippocampus library was then screened using a combination of the clone encoding β_{2D} and a portion of the β_3 clone deposited under ATCC Accession No. 69048. Multiple hybridizing clones were isolated. Among these were clones designated β_{101} , β_{102} and β_{104} . β_{101} appears to encode the 5' end of a splice variant of β_2 , designated β_{2E} . β_{102} and β_{104} encode portions of the 3' end of β_2 .

It appears that the β_2 splice variants include nucleotides 182-2294 of SEQ ID No. 26 and differ only between

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the start codon and nucleotides that correspond to 212 of SEQ. ID No. 26.

EXAMPLE VIII: ISOLATION OF cDNA CLONES ENCODING HUMAN CALCIUM CHANNEL β_4 and β_3 SUBUNITS

A. Isolation of cDNA Clones Encoding a Human β_4 Subunit

A clone containing a translation initiation codon and approximately 60% of the β_4 coding sequence was obtained from a human cerebellum cDNA library (see nucleotides 1-894 of Sequence ID No. 27). To obtain DNA encoding the remaining 3' portion of the β_4 coding sequence, a human cerebellum cDNA library was screened for hybridization a nucleic acid amplification product under high stringency hybridization and wash conditions. Hybridizing clones are purified and characterized by restriction enzyme mapping and DNA sequence analysis to identify those that contain sequence corresponding to the 3' end of the β_4 subunit coding sequence and a termination codon. Selected clones are ligated to the clone containing the 5' half of the β_4 coding sequence at convenient restriction sites to generate a full-length cDNA encoding a β_4 subunit. The sequence of a full-length β_4 clone is set forth in SEQ ID No. 27; the amino acid sequence is set forth in SEQ ID No. 28.

B. Isolation of cDNA Clones Encoding a Human β_3 Subunit

Sequencing of clones isolated as described in Example III also revealed a clone encoding a human neuronal calcium channel β_3 subunit. This clone has been deposited as plasmid β_3 1.42 (ATCC Accession No. 69048).

To isolate a full-length cDNA clone encoding a complete β_3 subunit, a human hippocampus cDNA library (Stratagene, La Jolla, CA) was screened for hybridization to a 5' EcoRI-PstI fragment of the cDNA encoding β_{1-2} using lower stringency hybridization conditions (20% deionized formamide, 200 μ g/ml sonicated herring sperm DNA, 5X SSPE, 5X Denhardt's solution, 42° C) and wash conditions. One of the hybridizing clones contained both translation initiation and termination codons

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and encodes a complete β_3 subunit designated $\beta_{3,1}$ (Sequence ID No. 19). In vitro transcripts of the cDNA were prepared and injected into *Xenopus* oocytes along with transcripts of the α_{1B-1} and α_{2b} cDNAs using methods similiar to those described in Example IX.D. Two-electrode voltage clamp recordings of the oocytes revealed significant voltage-dependent inward Ba^{2+} currents.

An additional β_3 subunit-encoding clone, designated $\beta_{3,2}$, was obtained by screening a human cerebellum cDNA library for hybridization to the nucleic acid amplification product referred to in Example VIII.A. under lower stringency (20% deionized formamide, 200 μ g/ml sonicated herring sperm DNA, 5X SSPE, 5X Denhardt's solution, 42° C) hybridization and wash conditions. The 5' ends of this clone (Sequence ID No. 20, $\beta_{3,2}$) and the first β_3 subunit, designated $\beta_{3,1}$, (Sequence ID No. 19) differ at their 5' ends and are splice variants of the β_3 gene.

EXAMPLE IX: RECOMBINANT EXPRESSION OF HUMAN NEURONAL CALCIUM CHANNEL SUBUNIT-ENCODING cDNA AND RNA TRANSCRIPTS IN MAMMALIAN CELLS

A. Recombinant Expression of the Human Neuronal Calcium Channel α_2 subunit cDNA in DG44 Cells

1. Stable transfection of DG44 cells

DG44 cells [dhfr⁻ Chinese hamster ovary cells; see, e.g., Urlaub, G. et al. (1986) *Som. Cell Molec. Genet.* 12:555-566] obtained from Lawrence Chasin at Columbia University were stably transfected by CaPO₄ precipitation methods [Wigler et al. (1979) *Proc. Natl. Acad. Sci. USA* 76:1373-1376] with pSV2dhfr vector containing the human neuronal calcium channel α_2 -subunit cDNA (see Example IV) for polycistronic expression/selection in transfected cells. Transfectants were grown on 10% DMEM medium without hypoxanthine or thymidine in order to select cells that had incorporated the expression vector. Twelve transfectant cell lines were established as indicated by their ability to survive on this medium.

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2. Analysis of α_2 subunit cDNA expression in transfected DG44 cells

Total RNA was extracted according to the method of Birnboim [(1988) *Nuc. Acids Res.* 16:1487-1497] from four of the DG44 cell lines that had been stably transfected with pSV2dhfr containing the human neuronal calcium channel α_2 subunit cDNA. RNA (~15 μ g per lane) was separated on a 1% agarose formaldehyde gel, transferred to nitrocellulose and hybridized to the random-primed human neuronal calcium channel α_2 cDNA (hybridization: 50% formamide, 5 x SSPE, 5 x Denhardt's, 42° C.; wash :0.2 x SSPE, 0.1% SDS, 65° C.). Northern blot analysis of total RNA from four of the DG44 cell lines that had been stably transfected with pSV2dhfr containing the human neuronal calcium channel α_2 subunit cDNA revealed that one of the four cell lines contained hybridizing mRNA the size expected for the transcript of the α_2 subunit cDNA (5000 nt based on the size of the cDNA) when grown in the presence of 10 mM sodium butyrate for two days. Butyrate nonspecifically induces transcription and is often used for inducing the SV40 early promoter [Gorman, C. and Howard, B. (1983) *Nucleic Acids Res.* 11:1631]. This cell line, 44 α_2 -9, also produced mRNA species smaller (several species) and larger (6800 nt) than the size expected for the transcript of the α_2 cDNA (5000 nt) that hybridized to the α_2 cDNA-based probe. The 5000- and 6800-nt transcripts produced by this transfectant should contain the entire α_2 subunit coding sequence and therefore should yield a full-length α_2 subunit protein. A weakly hybridizing 8000-nucleotide transcript was present in untransfected and transfected DG44 cells. Apparently, DG44 cells transcribe a calcium channel α_2 subunit or similar gene at low levels. The level of expression of this endogenous α_2 subunit transcript did not appear to be affected by exposing the cells to butyrate before isolation of RNA for northern analysis.

Total protein was extracted from three of the DG44 cell lines that had been stably transfected with pSV2dhfr

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containing the human neuronal calcium channel α_2 subunit cDNA. Approximately 10^7 cells were sonicated in 300 μ l of a solution containing 50 mM HEPES, 1 mM EDTA, 1 mM PMSF. An equal volume of 2x loading dye [Laemmli, U.K. (1970). *Nature* 227:680] was added to the samples and the protein was subjected to electrophoresis on an 8% polyacrylamide gel and then electrotransferred to nitrocellulose. The nitrocellulose was incubated with polyclonal guinea pig antisera (1:200 dilution) directed against the rabbit skeletal muscle calcium channel α_2 subunit (obtained from K. Campbell, University of Iowa) followed by incubation with [125 I]-protein A. The blot was exposed to X-ray film at -70° C. Reduced samples of protein from the transfected cells as well as from untransfected DG44 cells contained immunoreactive protein of the size expected for the α_2 subunit of the human neuronal calcium channel (130-150 kDa). The level of this immunoreactive protein was higher in 44 α_2 -9 cells that had been grown in the presence of 10 mM sodium butyrate than in 44 α_2 -9 cells that were grown in the absence of sodium butyrate. These data correlate well with those obtained in northern analyses of total RNA from 44 α_2 -9 and untransfected DG44 cells. Cell line 44 α_2 -9 also produced a 110 kD immunoreactive protein that may be either a product of proteolytic degradation of the full-length α_2 subunit or a product of translation of one of the shorter (<5000 nt) mRNAs produced in this cell line that hybridized to the α_2 subunit cDNA probe.

B. Expression of DNA encoding human neuronal calcium channel α_1 , α_2 and β_1 subunits in HEK cells

Human embryonic kidney cells (HEK 293 cells) were transiently and stably transfected with human neuronal DNA encoding calcium channel subunits. Individual transfectants were analyzed electrophysiologically for the presence of voltage-activated barium currents and functional recombinant voltage-dependent calcium channels were.

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1. Transfection of HEK 293 cells

Separate expression vectors containing DNA encoding human neuronal calcium channel α_{1D} , α_2 and β_1 subunits, plasmids pVDCCIII(A), pHBCaCH α_2 A, and pHBCaCH β_{1a} RBS(A), respectively, were constructed as described in Examples II.A.3, IV.B. and III.B.3., respectively. These three vectors were used to transiently co-transfect HEK 293 cells. For stable transfection of HEK 293 cells, vector pHBCaCH β_{1b} RBS(A) (Example III.B.3.) was used in place of pHBCaCH β_{1a} RBS(A) to introduce the DNA encoding the β_1 subunit into the cells along with pVDCCIII(A) and pHBCaCH α_2 A.

a. Transient transfection

Expression vectors pVDCCIII(A), pHBCaCH α_2 A and pHBCaCH β_{1a} RBS(A) were used in two sets of transient transfections of HEK 293 cells (ATCC Accession No. CRL1573). In one transfection procedure, HEK 293 cells were transiently cotransfected with the α_1 subunit cDNA expression plasmid, the α_2 subunit cDNA expression plasmid, the β_1 subunit cDNA expression plasmid and plasmid pCMV β gal (Clontech Laboratories, Palo Alto, CA). Plasmid pCMV β gal contains the lacZ gene (encoding *E. coli* β -galactosidase) fused to the cytomegalovirus (CMV) promoter and was included in this transfection as a marker gene for monitoring the efficiency of transfection. In the other transfection procedure, HEK 293 cells were transiently co-transfected with the α_1 subunit cDNA expression plasmid pVDCCIII(A) and pCMV β gal. In both transfections, $2-4 \times 10^6$ HEK 293 cells in a 10-cm tissue culture plate were transiently co-transfected with 5 μ g of each of the plasmids included in the experiment according to standard CaPO₄ precipitation transfection procedures (Wigler et al. (1979) *Proc. Natl. Acad. Sci. USA* 76:1373-1376). The transfectants were analyzed for β -galactosidase expression by direct staining of the product of a reaction involving β -galactosidase and the X-gal substrate [Jones, J.R. (1986) *EMBO* 5:3133-3142] and by measurement of β -galactosidase activity [Miller, J.H. (1972) *Experiments in Molecular Genetics*, pp.

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352-355, Cold Spring Harbor Press]. To evaluate subunit cDNA expression in these transfectants, the cells were analyzed for subunit transcript production (northern analysis), subunit protein production (immunoblot analysis of cell lysates) and functional calcium channel expression (electrophysiological analysis).

b. Stable transfection

HEK 293 cells were transfected using the calcium phosphate transfection procedure [Current Protocols in Molecular Biology, Vol. 1, Wiley Inter-Science, Supplement 14, Unit 9.1.1-9.1.9 (1990)]. Ten-cm plates, each containing one-to-two million HEK 293 cells, were transfected with 1 ml of DNA/calcium phosphate precipitate containing 5 μ g pVDCIII(A), 5 μ g pHBCaCH α_2 A, 5 μ g pHBCaCH β_{1B} RBS(A), 5 μ g pCMVBgal and 1 μ g pSV2neo (as a selectable marker). After 10-20 days of growth in media containing 500 μ g G418, colonies had formed and were isolated using cloning cylinders.

2. Analysis of HEK 293 cells transiently transfected with DNA encoding human neuronal calcium channel subunits

a. Analysis of β -galactosidase expression

Transient transfectants were assayed for β -galactosidase expression by β -galactosidase activity assays (Miller, J.H., (1972) Experiments in Molecular Genetics, pp. 352-355, Cold Spring Harbor Press) of cell lysates (prepared as described in Example VII.A.2) and staining of fixed cells (Jones, J.R. (1986) *EMBO* 5:3133-3142). The results of these assays indicated that approximately 30% of the HEK 293 cells had been transfected.

b. Northern analysis

PolyA+ RNA was isolated using the Invitrogen Fast Trak Kit (Invitrogen, San Diego, CA) from HEK 293 cells transiently transfected with DNA encoding each of the α_1 , α_2 and β_1 subunits and the *lacZ* gene or the α_1 subunit and the *lacZ* gene. The RNA was subjected to electrophoresis on an agarose gel and transferred to nitrocellulose. The nitrocellulose was then hybridized with one or more of the following radiolabeled

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probes: the *lacZ* gene, human neuronal calcium channel α_{1b} subunit-encoding cDNA, human neuronal calcium channel α_2 subunit-encoding cDNA or human neuronal calcium channel β_1 subunit-encoding cDNA. Two transcripts that hybridized with the α_1 subunit-encoding cDNA were detected in HEK 293 cells transfected with the DNA encoding the α_1 , α_2 , and β_1 subunits and the *lacZ* gene as well as in HEK 293 cells transfected with the α_1 subunit cDNA and the *lacZ* gene. One mRNA species was the size expected for the transcript of the α_1 subunit cDNA (8000 nucleotides). The second RNA species was smaller (4000 nucleotides) than the size expected for this transcript. RNA of the size expected for the transcript of the *lacZ* gene was detected in cells transfected with the α_1 , α_2 , and β_1 subunit-encoding cDNA and the *lacZ* gene and in cells transfected with the α_1 subunit cDNA and the *lacZ* gene by hybridization to the *lacZ* gene sequence.

RNA from cells transfected with the α_1 , α_2 and β_1 subunit-encoding cDNA and the *lacZ* gene was also hybridized with the α_2 and β_1 subunit cDNA probes. Two mRNA species hybridized to the α_2 subunit cDNA probe. One species was the size expected for the transcript of the α_2 subunit cDNA (4000 nucleotides). The other species was larger (6000 nucleotides) than the expected size of this transcript. Multiple RNA species in the cells co-transfected with α_1 , α_2 and β_1 subunit-encoding cDNA and the *lacZ* gene hybridized to the β_1 subunit cDNA probe. Multiple β subunit transcripts of varying sizes were produced since the β subunit cDNA expression vector contains two potential polyA⁺ addition sites.

c. Electrophysiological analysis

Individual transiently transfected HEK 293 cells were assayed for the presence of voltage-dependent barium currents using the whole-cell variant of the patch clamp technique [Hamill et al. (1981). *Pflugers Arch.* 391:85-100]. HEK 293 cells transiently transfected with pCMV β gal only were assayed for barium currents as a negative control in these experiments. The cells were placed in a bathing solution that

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contained barium ions to serve as the current carrier. Choline chloride, instead of NaCl or KCl, was used as the major salt component of the bath solution to eliminate currents through sodium and potassium channels. The bathing solution contained 1 mM MgCl₂, and was buffered at pH 7.3 with 10 mM HEPES (pH adjusted with sodium or tetraethylammonium hydroxide). Patch pipettes were filled with a solution containing 135 mM CsCl, 1 mM MgCl₂, 10 mM glucose, 10 mM EGTA, 4 mM ATP and 10 mM HEPES (pH adjusted to 7.3 with tetraethylammonium hydroxide). Cesium and tetraethylammonium ions block most types of potassium channels. Pipettes were coated with Sylgard (Dow-Corning, Midland, MI) and had resistances of 1-4 megohm. Currents were measured through a 500 megohm headstage resistor with the Axopatch IC (Axon Instruments, Foster City, CA) amplifier, interfaced with a Labmaster (Scientific Solutions, Solon, OH) data acquisition board in an IBM-compatible PC. PClamp (Axon Instruments) was used to generate voltage commands and acquire data. Data were analyzed with pClamp or Quattro Professional (Borland International, Scotts Valley, CA) programs.

To apply drugs, "puffer" pipettes positioned within several micrometers of the cell under study were used to apply solutions by pressure application. The drugs used for pharmacological characterization were dissolved in a solution identical to the bathing solution. Samples of a 10 mM stock solution of Bay K 8644 (RBI, Natick, MA), which was prepared in DMSO, were diluted to a final concentration of 1 μ M in 15 mM Ba²⁺-containing bath solution before they were applied.

Twenty-one negative control HEK 293 cells (transiently transfected with the lacZ gene expression vector pCMV β gal only) were analyzed by the whole-cell variant of the patch clamp method for recording currents. Only one cell displayed a discernable inward barium current; this current was not affected by the presence of 1 μ M Bay K 8644. In addition, application of Bay K 8644 to four cells that did not display Ba²⁺ currents did not result in the appearance of any currents.

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Two days after transient transfection of HEK 293 cells with α_1 , α_2 , and β_1 subunit-encoding cDNA and the lacZ gene, individual transfectants were assayed for voltage-dependent barium currents. The currents in nine transfectants were recorded. Because the efficiency of transfection of one cell can vary from the efficiency of transfection of another cell, the degree of expression of heterologous proteins in individual transfectants varies and some cells do not incorporate or express the foreign DNA. Inward barium currents were detected in two of these nine transfectants. In these assays, the holding potential of the membrane was -90 mV. The membrane was depolarized in a series of voltage steps to different test potentials and the current in the presence and absence of 1 μ M Bay K 8644 was recorded. The inward barium current was significantly enhanced in magnitude by the addition of Bay K 8644. The largest inward barium current (~160 pA) was recorded when the membrane was depolarized to 0 mV in the presence of 1 μ M Bay K 8644. A comparison of the I-V curves, generated by plotting the largest current recorded after each depolarization versus the depolarization voltage, corresponding to recordings conducted in the absence and presence of Bay K 8644 illustrated the enhancement of the voltage-activated current in the presence of Bay K 8644.

Pronounced tail currents were detected in the tracings of currents generated in the presence of Bay K 8644 in HEK 293 cells transfected with α_1 , α_2 and β_1 subunit-encoding cDNA and the lacZ gene, indicating that the recombinant calcium channels responsible for the voltage-activated barium currents recorded in this transfected appear to be DHP-sensitive.

The second of the two transfected cells that displayed inward barium currents expressed a ~50 pA current when the membrane was depolarized from -90 mV. This current was nearly completely blocked by 200 μ M cadmium, an established calcium channel blocker.

Ten cells that were transiently transfected with the DNA encoding the α_1 subunit and the lacZ gene were analyzed by

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whole-cell patch clamp methods two days after transfection. One of these cells displayed a 30 pA inward barium current. This current amplified 2-fold in the presence of 1 μ M Bay K 8644. Furthermore, small tail currents were detected in the presence of Bay K 8644. These data indicate that expression of the human neuronal calcium channel α_{1D} subunit-encoding cDNA in HEK 293 yields a functional DHP-sensitive calcium channel.

3. Analysis of HEK 293 cells stably transfected with DNA encoding human neuronal calcium channel subunits

Individual stably transfected HEK 293 cells were assayed electrophysiologically for the presence of voltage-dependent barium currents as described for electrophysiological analysis of transiently transfected HEK 293 cells (see ExampI VII.B.2.c). In an effort to maximize calcium channel activity via cyclic-AMP-dependent kinase-mediated phosphorylation [Pelzer, et al. (1990) *Rev. Physiol. Biochem. Pharmacol.* 114:107-207], cAMP (Na salt, 250 μ M) was added to the pipet solution and forskolin (10 μ M) was added to the bath solution in some of the recordings. Qualitatively similar results were obtained whether these compounds were present or not.

Barium currents were recorded from stably transfected cells in the absence and presence of Bay K 8644 (1 μ M). When the cell was depolarized to -10 mV from a holding potential of -90 mV in the absence of Bay K 8644, a current of approximately 35pA with a rapidly deactivating tail current was recorded. During application of Bay K 8644, an identical depolarizing protocol elicited a current of approximately 75 pA, accompanied by an augmented and prolonged tail current. The peak magnitude of currents recorded from this same cell as a function of a series of depolarizing voltages were assessed. The responses in the presence of Bay K 8644 not only increased, but the entire current-voltage relation shifted about -10 mV. Thus, three typical hallmarks of Bay K 8644 action, namely increased current magnitude, prolonged tail currents, and negatively shifted activation voltage, were

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observed, clearly indicating the expression of a DHP-sensitive calcium channel in these stably transfected cells. No such effects of Bay K 8644 were observed in untransfected HEK 293 cells, either with or without cAMP or forskolin.

C. Use of pCMV-based vectors and pcDNA1-based vectors for expression of DNA encoding human neuronal calcium channel subunits

1. Preparation of constructs

Additional expression vectors were constructed using pCMV. The full-length α_{1D} cDNA from pVDCCIII(A) (see Example II.A.3.d), the full-length α_2 cDNA, contained on a 3600 bp *EcoRI* fragment from HBCaCH α_2 (see Example IV.B) and a full-length β_1 subunit cDNA from pHBCaCH β_{1D} RBS(A) (see Example III.B.3) were separately subcloned into plasmid pCMV β gal. Plasmid pCMV β gal was digested with *NotI* to remove the *lacZ* gene. The remaining vector portion of the plasmid, referred to as pCMV, was blunt-ended at the *NotI* sites. The full-length α_2 -encoding DNA and β_1 -encoding DNA, contained on separate *EcoRI* fragments, were isolated, blunt-ended and separately ligated to the blunt-ended vector fragment of pCMV locating the cDNAs between the CMV promoter and SV40 polyadenylation sites in pCMV. To ligate the α_{1D} -encoding cDNA with pCMV, the restriction sites in the polylinkers immediately 5' of the CMV promoter and immediately 3' of the SV40 polyadenylation site were removed from pCMV. A polylinker was added at the *NotI* site. The polylinker had the following sequence of restriction enzyme recognition sites:

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GGCCGC	EcoRI	Sali	PstI	EcoRV	HindIII	XbaII	GT
CG	site	site	site	site	site	site	CACCGG
							↑
NotI							Destroys Not

The α_{1D} -encoding DNA, isolated as a *Bam*HI/*Xho*I fragment from pVDCCIII(A), was then ligated to *Xba*II/*Sali*-digested pCMV to place it between the CMV promoter and SV40 polyadenylation site.

Plasmid pCMV contains the CMV promoter as does pcDNA1, but differs from pcDNA1 in the location of splice donor/splice acceptor sites relative to the inserted subunit-encoding DNA. After inserting the subunit-encoding DNA into pCMV, the splice donor/splice acceptor sites are located 3' of the CMV promoter and 5' of the subunit-encoding DNA start codon. After inserting the subunit-encoding DNA into pcDNA1, the splice donor/splice acceptor sites are located 3' of the subunit cDNA stop codon.

2. Transfection of HEK 293 cells

HEK 293 cells were transiently co-transfected with the α_{1D} , α_2 and β_1 subunit-encoding DNA in pCMV or with the α_{1D} , α_2 and β subunit-encoding DNA in pcDNA1 (vectors pVDCCIII(A), pHBCaCH α_2 A and pHBCaCH β_{1D} RBS(A), respectively), as described in Example VII.B.1.a. Plasmid pCMV β gal was included in each transfection as a measure of transfection efficiency. The results of β -galactosidase assays of the transfectants (see Example VII.B.2.), indicated that HEK 293 cells were transfected equally efficiently with pCMV- and pcDNA1-based plasmids. The pcDNA1-based plasmids, however, are presently preferred for expression of calcium channel receptors.

D. Expression in *Xenopus laevis* oocytes of RNA encoding human neuronal calcium channel subunits

Various combinations of the transcripts of DNA encoding the human neuronal α_{1D} , α_2 and β_1 subunits prepared in vitro were injected into *Xenopus laevis* oocytes. Those injected with combinations that included α_{1D} exhibited voltage-activated barium currents.

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1. Preparation of transcripts

Transcripts encoding the human neuronal calcium channel α_{1D} , α_2 and β_1 subunits were synthesized according to the instructions of the mCAP mRNA CAPPING KIT (Stratagene, La Jolla, CA catalog #200350). Plasmids pVDCC III.RBS(A), containing pcDNA1 and the α_{1D} cDNA that begins with a ribosome binding site and the eighth ATG codon of the coding sequence (see Example III.A.3.d), plasmid pHBCaCH α_2 A containing pcDNA1 and an α_2 subunit cDNA (see Example IV), and plasmid pHBCaCH β_{1D} RBS(A) containing pcDNA1 and the β_1 DNA lacking intron sequence and containing a ribosome binding site (see Example III), were linearized by restriction digestion. The α_{1D} cDNA- and α_2 subunit-encoding plasmids were digested with *XhoI*, and the β_1 subunit- encoding plasmid was digested with *EcoRV*. The DNA insert was transcribed with T7 RNA polymerase.

2. Injection of oocytes

Xenopus laevis oocytes were isolated and defolliculated by collagenase treatment and maintained in 100 mM NaCl, 2 mM KCl, 1.8 mM CaCl₂, 1 mM MgCl₂, 5 mM HEPES, pH 7.6, 20 μ g/ml ampicillin and 25 μ g/ml streptomycin at 19-25°C for 2 to 5 days after injection and prior to recording. For each transcript that was injected into the oocyte, 6 ng of the specific mRNA was injected per cell in a total volume of 50 nl.

3. Intracellular voltage recordings

Injected oocytes were examined for voltage-dependent barium currents using two-electrode voltage clamp methods [Dascal, N. (1987) *CRC Crit. Rev. Biochem.* 22:317]. The pClamp (Axon Instruments) software package was used in conjunction with a Labmaster 125 kHz data acquisition interface to generate voltage commands and to acquire and analyze data. Quattro Professional was also used in this analysis. Current signals were digitized at 1-5 kHz, and filtered appropriately. The bath solution contained of the following: 40 mM BaCl₂, 36 mM tetraethylammonium chloride

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(TEA-Cl), 2 mM KCl, 5 mM 4-aminopyridine, 0.15 mM niflumic acid, 5 mM HEPES, pH 7.6.

a. Electrophysiological analysis of oocytes injected with transcripts encoding the human neuronal calcium channel α_1 , α_2 , and β_1 -subunits

Uninjected oocytes were examined by two-electrode voltage clamp methods and a very small (25 nA) endogenous inward Ba^{2+} current was detected in only one of seven analyzed cells.

Oocytes coinjected with α_{1D} , α_2 , and β_1 subunit transcripts expressed sustained inward barium currents upon depolarization of the membrane from a holding potential of -90 mV or -50 mV (154 ± 129 nA, $n=21$). These currents typically showed little inactivation when test pulses ranging from 140 to 700 msec. were administered. Depolarization to a series of voltages revealed currents that first appeared at approximately -30 mV and peaked at approximately 0 mV.

Application of the DHP Bay K 8644 increased the magnitude of the currents, prolonged the tail currents present upon repolarization of the cell and induced a hyperpolarizing shift in current activation. Bay K 8644 was prepared fresh from a stock solution in DMSO and introduced as a 10x concentrate directly into the 60 μl bath while the perfusion pump was turned off. The DMSO concentration of the final diluted drug solutions in contact with the cell never exceeded 0.1%. Control experiments showed that 0.1% DMSO had no effect on membrane currents.

Application of the DHP antagonist nifedipine (stock solution prepared in DMSO and applied to the cell as described for application of Bay K 8644) blocked a substantial fraction ($91 \pm 6\%$, $n=7$) of the inward barium current in oocytes coinjected with transcripts of the α_{1D} , α_2 and β_1 subunits. A residual inactivating component of the inward barium current typically remained after nifedipine application. The inward barium current was blocked completely by 50 μM Cd^{2+} , but only approximately 15% by 100 μM Ni^{2+} .

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The effect of ω CgTX on the inward barium currents in oocytes co-injected with transcripts of the α_{1D} , α_2 , and β_1 subunits was investigated. ω CgTX (Bachem, Inc., Torrance CA) was prepared in the 15 mM BaCl₂ bath solution plus 0.1% cytochrome C (Sigma) to serve as a carrier protein. Control experiments showed that cytochrome C had no effect on currents. A series of voltage pulses from a -90 mV holding potential to 0 mV were recorded at 20 msec. intervals. To reduce the inhibition of ω CgTX binding by divalent cations, recordings were made in 15 mM BaCl₂, 73.5 mM tetraethylammonium chloride, and the remaining ingredients identical to the 40 mM Ba²⁺ recording solution. Bay K 8644 was applied to the cell prior to addition to ω CgTX in order to determine the effect of ω CgTX on the DHP-sensitive current component that was distinguished by the prolonged tail currents. The inward barium current was blocked weakly ($54 \pm 29\%$, $n=7$) and reversibly by relatively high concentrations (10-15 μ M) of ω CgTX. The test currents and the accompanying tail currents were blocked progressively within two to three minutes after application of ω CgTX, but both recovered partially as the ω CgTX was flushed from the bath.

b. Analysis of oocytes injected with only a transcripts encoding the human neuronal calcium channel α_{1D} or transcripts encoding an α_{1D} and other subunits

The contribution of the α_2 and β_1 subunits to the inward barium current in oocytes injected with transcripts encoding the α_{1D} , α_2 and β_1 subunits was assessed by expression of the α_{1D} subunit alone or in combination with either the β_1 subunit or the α_2 subunit. In oocytes injected with only the transcript of a α_{1D} cDNA, no Ba²⁺ currents were detected ($n=3$). In oocytes injected with transcripts of α_{1D} and β_1 cDNAs, small (108 ± 39 nA) Ba²⁺ currents were detected upon depolarization of the membrane from a holding potential of -90 mV that resembled the currents observed in cells injected with transcripts of α_{1D} , α_2 and β_1 cDNAs, although the magnitude of

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the current was less. In two of the four oocytes injected with transcripts of the α_{1D} -encoding and β_1 -encoding DNA, the Ba^{2+} currents exhibited a sensitivity to Bay K 8644 that was similar to the Bay K 8644 sensitivity of Ba^{2+} currents expressed in oocytes injected with transcripts encoding the α_{1D} , α_1 -, α_2 - and β_1 subunits.

Three of five oocytes injected with transcripts encoding the α_{1D} and α_2 subunits exhibited very small Ba^{2+} currents (15-30 nA) upon depolarization of the membrane from a holding potential of -90 mV. These barium currents showed little or no response to Bay K 8644.

c. Analysis of oocytes injected with transcripts encoding the human neuronal calcium channel α_2 and/or β_1 subunit

To evaluate the contribution of the α_{1D} α_1 -subunit to the inward barium currents detected in oocytes co-injected with transcripts encoding the α_{1D} , α_2 and β_1 subunits, oocytes injected with transcripts encoding the human neuronal calcium channel α_2 and/or β_1 subunits were assayed for barium currents. Oocytes injected with transcripts encoding the α_2 subunit displayed no detectable inward barium currents (n=5). Oocytes injected with transcripts encoding a β_1 subunit displayed measurable (54 ± 23 nA, n=5) inward barium currents upon depolarization and oocytes injected with transcripts encoding the α_2 and β_1 subunits displayed inward barium currents that were approximately 50% larger (80 ± 61 nA, n=18) than those detected in oocytes injected with transcripts of the β_1 -encoding DNA only.

The inward barium currents in oocytes injected with transcripts encoding the β_1 subunit or α_2 and β_1 subunits typically were first observed when the membrane was depolarized to -30 mV from a holding potential of -90 mV and peaked when the membrane was depolarized to 10 to 20 mV. Macroscopically, the currents in oocytes injected with transcripts encoding the α_2 and β_1 subunits or with transcripts encoding the β_1 subunit were indistinguishable. In contrast to the currents in oocytes co-injected with transcripts of α_{1D} ,

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α_2 and β_1 subunit cDNAs, these currents showed a significant inactivation during the test pulse and a strong sensitivity to the holding potential. The inward barium currents in oocytes co-injected with transcripts encoding the α_2 and β_1 subunits usually inactivated to 10-60% of the peak magnitude during a 140-msec pulse and were significantly more sensitive to holding potential than those in oocytes co-injected with transcripts encoding the α_{1D} , α_2 and β_1 subunits. Changing the holding potential of the membranes of oocytes co-injected with transcripts encoding the α_2 and β_1 subunits from -90 to -50 mV resulted in an approximately 81% (n=11) reduction in the magnitude of the inward barium current of these cells. In contrast, the inward barium current measured in oocytes co-injected with transcripts encoding the α_{1D} , α_2 and β_1 subunits were reduced approximately 24% (n=11) when the holding potential was changed from -90 to -50 mV.

The inward barium currents detected in oocytes injected with transcripts encoding the α_2 and β_1 subunits were pharmacologically distinct from those observed in oocytes co-injected with transcripts encoding the α_{1D} , α_2 and β_1 subunits. Oocytes injected with transcripts encoding the α_2 and β_1 subunits displayed inward barium currents that were insensitive to Bay K 8644 (n=11). Nifedipine sensitivity was difficult to measure because of the holding potential sensitivity of nifedipine and the current observed in oocytes injected with transcripts encoding the α_2 and β_1 subunits. Nevertheless, two oocytes that were co-injected with transcripts encoding the α_2 and β_1 subunits displayed measurable (25 to 45 nA) inward barium currents when depolarized from a holding potential of -50 mV. These currents were insensitive to nifedipine (5 to 10 μ M). The inward barium currents in oocytes injected with transcripts encoding the α_2 and β_1 subunits showed the same sensitivity to heavy metals as the currents detected in oocytes injected with transcripts encoding the α_{1D} , α_2 and β_1 subunits.

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The inward barium current detected in oocytes injected with transcripts encoding the human neuronal α_2 and β_1 subunits has pharmacological and biophysical properties that resemble calcium currents in uninjected *Xenopus* oocytes. Because the amino acids of this human neuronal calcium channel β_1 subunit lack hydrophobic segments capable of forming transmembrane domains, it is unlikely that recombinant β_1 subunits alone can form an ion channel. It is more probable that a homologous endogenous α_1 subunit exists in oocytes and that the activity mediated by such an α_1 subunit is enhanced by expression of a human neuronal β_1 subunit.

E. Expression of DNA encoding human neuronal calcium channel α_{1B} , α_2 , and β_{1-2} subunits in HEK cells

1. Transfection of HEK cells

The transient expression of the human neuronal α_{1B-1} , α_{2B} and β_{1-2} subunits was studied in HEK293 cells. The HEK293 cells were grown as a monolayer culture in Dulbecco's modified Eagle's medium (Gibco) containing 5% defined-supplemented bovine calf serum (Hyclone) plus penicillin G (100 U/ml) and streptomycin sulfate (100 μ g/ml). HEK293 cell transfections were mediated by calcium phosphate as described above. Transfected cells were examined for inward Ba^{2+} currents (I_{Ba}) mediated by voltage-dependent Ca^{2+} channels.

Cells were transfected (2×10^6 per polylysine-coated plate. Standard transfections (10-cm dish) contained 8 μ g of pcDNA α_{1B-1} , 5 μ g of pHBCaCH α_2 A, 2 μ g pHBCaCH β_{1B} RBS(A) (see, Examples II.A.3, IV.B. and III) and 2 μ g of CMV β (Clontech) β -galactosidase expression plasmid, and pUC18 to maintain a constant mass of 20 μ g/ml. Cells were analyzed 48 to 72 hours after transfection. Transfection efficiencies ($\pm 10\%$), which were determined by in situ histochemical staining for β -galactosidase activity (Sanes et al. (1986) *EMBO J.*, 5:3133), generally were greater than 50%.

2. Electrophysiological analysis of transfectant currents

a. Materials and methods

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Properties of recombinantly expressed Ca^{2+} channels were studied by whole cell patch-clamp techniques. Recordings were performed on transfected HEK293 cells 2 to 3 days after transfection. Cells were plated at 100,000 to 300,000 cells per polylysine-coated, 35-mm tissue culture dishes (Falcon, Oxnard, CA) 24 hours before recordings. Cells were perfused with 15 mM BaCl_2 , 125 mM choline chloride, 1 mM MgCl_2 , and 10 mM Hepes (pH = 7.3) adjusted with tetraethylammonium hydroxide (bath solution). Pipettes were filled with 135 mM CsCl , 10 mM EGTA, 10 mM Hepes, 4 mM Mg-adenosine triphosphate (pH = 7.5) adjusted with tetraethylammonium hydroxide. Sylgard (Dow-Corning, Midland, MI)-coated, fire-polished, and filled pipettes had resistances of 1 to 2 megohm before gigohm seals were established to cells.

Bay K 8644 and nifedipine (Research Biochemicals, Natick, MA) were prepared from stock solutions (in dimethyl sulfoxide) and diluted into the bath solution. The dimethyl sulfoxide concentration in the final drug solutions in contact with the cells never exceeded 0.1%. Control experiments showed that 0.1% dimethyl sulfoxide had no effect on membrane currents. ωCgTX (Bachem, Inc., Torrance CA) was prepared in the 15 mM BaCl_2 bath solution plus 0.1% cytochrome C (Sigma, St. Louis MO) to serve as a carrier protein. Control experiments showed that cytochrome C had no effect on currents. These drugs were dissolved in bath solution, and continuously applied by means of puffer pipettes as required for a given experiment. Recordings were performed at room temperature (22° to 25°C). Series resistance compensation (70 to 85%) was employed to minimize voltage error that resulted from pipette access resistance, typically 2 to 3.5 megohm. Current signals were filtered (-3 dB, 4-pole Bessel) at a frequency of 1/4 to 1/5 the sampling rate, which ranged from 0.5 to 3 kHz. Voltage commands were generated and data were acquired with CLAMPEX (pClamp, Axon Instruments, Foster City, CA). All reported data are corrected for linear leak and capacitive

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components. Exponential fitting of currents was performed with CLAMPFIT (Axon Instruments, Foster City, CA).

b. Results

Transfectants were examined for inward Ba^{2+} currents (I_{Ba}). Cells cotransfected with DNA encoding $\alpha_{1\text{B}-1}$, $\alpha_{2\text{b}}$, and β_{1-2} subunits expressed high-voltage-activated Ca^{2+} channels. I_{Ba} first appeared when the membrane was depolarized from a holding potential of -90 mV to -20 mV and peaked in magnitude at 10 mV. Thirty-nine of 95 cells (12 independent transfections) had I_{Ba} that ranged from 30 to 2700 pA, with a mean of 433 pA. The mean current density was 26 pA/pF, and the highest density was 150 pA/pF. The I_{Ba} typically increased by 2- to 20-fold during the first 5 minutes of recording. Repeated depolarizations during long records often revealed rundown of I_{Ba} usually not exceeding 20% within 10 min. I_{Ba} typically activated within 10 ms and inactivated with both a fast time constant ranging from 46 to 105 ms and a slow time constant ranging from 291 to 453 ms ($n = 3$). Inactivation showed a complex voltage dependence, such that I_{Ba} elicited at ≥ 20 mV inactivated more slowly than I_{Ba} elicited at lower test voltages, possibly a result of an increase in the magnitude of slow compared to fast inactivation components at higher test voltages.

Recombinant $\alpha_{1\text{B}-1}\alpha_{2\text{b}}\beta_{1-2}$ channels were sensitive to holding potential. Steady-state inactivation of I_{Ba} , measured after a 30- to 60-s conditioning at various holding potentials, was approximately 50% at holding potential between -60 and -70 mV and approximately 90% at -40 mV. Recovery of I_{Ba} from inactivation was usually incomplete, measuring 55 to 75% of the original magnitude within 1 min. after the holding potential was returned to more negative potentials, possibly indicating some rundown or a slow recovery rate.

Recombinant $\alpha_{1\text{B}-1}\alpha_{2\text{b}}\beta_{1-2}$ channels were also blocked irreversibly by ω -CgTx concentrations ranging from 0.5 to 10 μM during the time scale of the experiments. Application of 5 μM toxin ($n = 7$) blocked the activity completely within

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2 min., and no recovery of I_{Ba} was observed after washing ω -CgTx from the bath for up to 15 min. d^{2+} blockage (50 μ M) was rapid, complete, and reversible; the DHPs Bay K 8644 (1 μ M; $n = 4$) or nifedipine (5 μ M; $n = 3$) had no discernable effect.

Cells cotransfected with DNA encoding α_{1B-1} , α_{2b} , and β_{1-2} subunits predominantly displayed a single class of saturable, high-affinity ω -CgTx binding sites. The determined dissociation constant (K_d) value was 54.6 ± 14.5 pM ($n = 4$). Cells transfected with the vector containing only β -galactosidase-encoding DNA or $\alpha_{2b}\beta$ -encoding DNA showed no specific binding. The binding capacity (B_{max}) of the $\alpha_{1B-1}\alpha_{2b}\beta$ -transfected cells was $28,710 \pm 11,950$ sites per cell ($n = 4$).

These results demonstrate that $\alpha_{1B-1}\alpha_{2b}\beta_{1-2}$ -transfected cells express high-voltage-activated, inactivating Ca^{2+} channel activity that is irreversibly blocked by ω -CgTx, insensitive to DHPs, and sensitive to holding potential. The activation and inactivation kinetics and voltage sensitivity of the channel formed in these cells are generally consistent with previous characterizations of neuronal N-type Ca^{2+} channels.

F. Expression of DNA encoding human neuronal calcium channel α_{1B-1} , α_{1B-2} , α_{2b} , β_{1-2} and β_{1-3} subunits in HEK cells

Significant Ba^{2+} currents were not detected in untransfected HEK293 cells. Furthermore, untransfected HEK293 cells do not express detectable ω -CgTx GVIA binding sites.

In order to approximate the expression of a homogeneous population of trimeric α_{1B} , α_{2b} and β_1 protein complexes in transfected HEK293 cells, the α_{1B} , α_{2b} and β_1 expression levels were altered. The efficiency of expression and assembly of channel complexes at the cell surface were optimized by adjusting the molar ratio of α_{1B} , α_{2b} and β_1 expression plasmids used in the transfections. The transfectants were analyzed for mRNA levels, ω -CgTx GVIA binding and Ca^{2+} channel current density in order to determine near optimal channel expression in the absence of immunological reagents for evaluating

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protein expression. Higher molar ratios of α_{2b} appeared to increase calcium channel activity.

1. Transfections

HEK293 cells were maintained in DMEM (Gibco #320-1965AJ), 5.5% Defined/Supplemented bovine calf serum (Hyclone #A-2151-L), 100 U/ml penicillin G and 100 μ g/ml streptomycin. Ca^{2+} -phosphate based transient transfections were performed and analyzed as described above. Cells were co-transfected with either 8 μ g pCDNA α_{1B-1} (described in Example II.C), 5 μ g pHBCaCH α_2A (see, Example IV.B.), 2 μ g pHBCaCH β_{1B} RBS(A) (β_{1-2} expression plasmid; see Examples III.A. and IX.E.), and 2 μ g pCMV β -gal [Clontech, Palo Alto, CA] (2:1.8:1 molar ratio of Ca^{2+} channel subunit expression plasmids) or with 3 μ g pCDNA α_{1B-1} or pCDNA α_{1B-2} , 11.25 μ g pHBCaCH α_2A , 0.75 or 1.0 μ g pHBCaCH β_{1B} RBS(A) or pCDNA β_{1-3} , and 2 μ g pCMV β -gal (2:10.9:1 molar ratio of Ca^{2+} channel subunit expression plasmids). Plasmid pCMV β -gal, a β -galactosidase expression plasmid, was included in the transfections as a marker to permit transfection efficiency estimates by histochemical staining. When less than three subunits were expressed, pCMVPL2, a pCMV promoter-containing vector that lacks a cDNA insert, was substituted to maintain equal moles of pCMV-based DNA in the transfection. pUC18 DNA was used to maintain the total mass of DNA in the transfection at 20 μ g/plate.

RNA from the transfected cells was analyzed by Northern blot analysis for calcium channel subunit mRNA expression using random primed ^{32}P -labeled subunit specific probes. HEK293 cells co-transfected with α_{1B-1} , α_{2b} and β_{1-2} expression plasmids (8, 5 and 2 μ g, respectively; molar ratio = 2:1.8:1) did not express equivalent levels of each Ca^{2+} channel subunit mRNA. Relatively high levels of α_{1B-1} and β_{1-2} mRNAs were expressed, but significantly lower levels of α_{2b} mRNA were expressed. Based on autoradiograph exposures required to produce equivalent signals for all three mRNAs, α_{2b} transcript levels were estimated to be 5 to 10 times lower than α_{1B-1} and

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β_{1-2} transcript levels. Untransfected HEK293 cells did not express detectable levels of α_{1B-1} , α_{2b} , or β_{1-2} mRNAs.

To achieve equivalent Ca^{2+} channel subunit mRNA expression levels, a series of transfections was performed with various amounts of α_{1B-1} , α_{2b} and β_{1-2} expression plasmids. Because the α_{1B-1} and β_{1-2} mRNAs were expressed at very high levels compared to α_{2b} mRNA, the mass of α_{1B-1} and β_{1-2} plasmids was lowered and the mass of α_{2b} plasmid was increased in the transfection experiments. Co-transfection with 3, 11.25 and 0.75 μg of α_{1B-1} , α_{2b} and β_{1-2} expression plasmids, respectively (molar ratio = 2:10.9:1), approached equivalent expression levels of each Ca^{2+} channel subunit mRNA. The relative molar quantity of α_{2b} expression plasmid to α_{1B-1} and β_{1-2} expression plasmids was increased 6-fold. The mass of α_{1B-1} and β_{1-2} plasmids in the transfection was decreased 2.67-fold and the mass of α_{2b} plasmid was increased 2.25-fold. The 6-fold molar increase of α_{2b} relative to α_{1B-1} and β_{1-2} required to achieve near equal abundance mRNA levels is consistent with the previous 5- to 10-fold lower estimate of relative α_{2b} mRNA abundance. ω -CgTx GVIA binding to cells transfected with various amounts of expression plasmids indicated that the 3, 11.25 and 0.75 μg of α_{1B-1} , α_{2b} and β_{1-2} plasmids, respectively, improved the level of cell surface expression of channel complexes. Further increases in the mass of α_{2b} and β_{1-2} expression plasmids while α_{1B-1} was held constant, and alterations in the mass of the α_{1B-1} expression plasmid while α_{2b} and β_{1-2} were held constant, indicated that the cell surface expression of ω -CgTx GVIA binding sites per cell was nearly optimal. All subsequent transfections were performed with 3, 11.25 and 0.75 μg or 1.0 μg of α_{1B-1} or α_{1B-2} , α_{2b} and β_{1-2} or β_{1-3} expression plasmids, respectively.

2. ^{125}I - ω -CgTx GVIA binding to transfected cells

Statistical analysis of the K_d and B_{max} values was performed using one-way analysis of variance (ANOVA) followed by the Tukey-Kramer test for multiple pairwise comparisons ($p \leq 0.05$).

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Combinations of human voltage-dependent Ca^{2+} channel subunits, α_{1B-1} , α_{1B-2} , α_{2b} , β_{1-2} and β_{1-3} , were analyzed for saturation binding of ^{125}I - ω -CgTx GVIA. About 200,000 cells were used per assay, except for the α_{1B-1} , α_{1B-2} , $\alpha_{1B-1}\alpha_{2b}$ and $\alpha_{1B-2}\alpha_{2b}$ combinations which were assayed with 1×10^6 cells per tube. The transfected cells displayed a single-class of saturable, high-affinity binding sites. The values for the dissociation constants (K_d) and binding capacities (B_{max}) were determined for the different combinations. The results are summarized as follows:

Subunit Combination	K_d (pM)	B_{max} (sites/cell)
$\alpha_{1B-1}\alpha_{2b}\beta_{1-2}$	54.9 ± 11.1 (n=4)	$45,324 \pm 15,606$
$\alpha_{1B-1}\alpha_{2b}\beta_{1-3}$	53.2 ± 3.6 (n=3)	$91,004 \pm 37,654$
$\alpha_{1B-1}\beta_{1-2}$	17.9 ± 1.9 (n=3)	$5,756 \pm 2,163$
$\alpha_{1B-1}\beta_{1-3}$	17.9 ± 1.6 (n=3)	$8,729 \pm 2,980$
$\alpha_{1B-1}\alpha_{2b}$	84.6 ± 15.3 (n=3)	$2,256 \pm 356$
α_{1B-1}	31.7 ± 4.2 (n=3)	757 ± 128
$\alpha_{1B-2}\alpha_{2b}\beta_{1-2}$	53.0 ± 4.8 (n=3)	$19,371 \pm 3,798$
$\alpha_{1B-2}\alpha_{2b}\beta_{1-3}$	44.3 ± 8.1 (n=3)	$37,652 \pm 8,129$
$\alpha_{1B-2}\beta_{1-2}$	16.4 ± 1.2 (n=3)	$2,126 \pm 412$
$\alpha_{1B-2}\beta_{1-3}$	22.2 ± 5.8 (n=3)	$2,944 \pm 1,168$
$\alpha_{1B-2}\alpha_{2b}$	N.D.* (n=3)	N.D.
α_{1B-2}	N.D.	N.D.

* N.D. = not detectable

Cells transfected with subunit combinations lacking either the α_{1B-1} or the α_{1B-2} subunit did not exhibit any detectable ^{125}I - ω -CgTx GVIA binding (≤ 600 sites/cell). ^{125}I - ω -CgTx GVIA binding to HEK293 cells transfected with α_{1B-2} alone or $\alpha_{1B-2}\alpha_{2b}$ was too low for reliable Scatchard analysis of the data. Comparison of the K_d and B_{max} values revealed several relationships between specific combinations of subunits and the binding affinities and capacities of the transfected cells. In cells transfected with all three subunits, ($\alpha_{1B-1}\alpha_{2b}\beta_{1-2}$ -, $\alpha_{1B-1}\alpha_{2b}\beta_{1-3}$ -, $\alpha_{1B-2}\alpha_{2b}\beta_{1-2}$ -, or $\alpha_{1B-2}\alpha_{2b}\beta_{1-3}$ -transfectants) the K_d values were indistinguishable ($p > 0.05$), ranging from 44.3

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± 8.1 pM to 54.9 ± 11.1 pM. In cells transfected with two-subunit combinations lacking the α_{2b} subunit ($\alpha_{1B-1}\beta_{1-2}$, $\alpha_{1B-1}\beta_{1-3}$, $\alpha_{1B-2}\beta_{1-2}$ or $\alpha_{1B-2}\beta_{1-3}$) the K_d values were significantly lower than the three-subunit combinations ($p < 0.01$), ranging from 16.4 ± 1.2 to 22.2 ± 5.8 pM. Cells transfected with only the α_{1B-1} subunit had a K_d value of 31.7 ± 4.2 pM, a value that was not different from the two-subunit combinations lacking α_{2b} ($p < 0.05$). As with the comparison between the four $\alpha_{1B}\alpha_{2b}\beta_1$ versus $\alpha_{1B}\beta_1$ combinations, when the α_{1B-1} was co-expressed with α_{2b} , the K_d increased significantly ($p < 0.05$) from 31.7 ± 4.2 to 84.6 ± 5.3 pM. These data demonstrate that co-expression of the α_{2b} subunit with α_{1B-1} , $\alpha_{1B-1}\beta_{1-2}$, $\alpha_{1B-1}\beta_{1-3}$, $\alpha_{1B-2}\beta_{1-2}$ or $\alpha_{1B-2}\beta_{1-3}$ subunit combinations results in lower binding affinity of the cell surface receptors for ^{125}I - ω -CgTx GVIA. The B_{\max} values of cells transfected with various subunit combinations also differed considerably. Cells transfected with the α_{1B-1} subunit alone expressed a low but detectable number of binding sites (approximately 750 binding sites/cell). When the α_{1B-1} subunit was co-expressed with the α_{2b} subunit, the binding capacity increased approximately three-fold while co-expression of a β_{1-2} or β_{1-3} subunit with α_{1B-1} resulted in 8- to 10-fold higher expression of surface binding. Cells transfected with all three subunits expressed the highest number of cell surface receptors. The binding capacities of cells transfected with $\alpha_{1B-1}\alpha_{2b}\beta_{1-3}$ or $\alpha_{1B-2}\alpha_{2b}\beta_{1-3}$ combinations were approximately two-fold higher than the corresponding combinations containing the β_{1-2} subunit. Likewise, cells transfected with $\alpha_{1B-1}\alpha_{2b}\beta_{1-2}$ or $\alpha_{1B-1}\alpha_{2b}\beta_{1-3}$ combinations expressed approximately 2.5-fold more binding sites per cell than the corresponding combinations containing α_{1B-2} . In all cases, co-expression of the α_{2b} subunit with α_{1B} and β_1 increased the surface receptor density compared to cells transfected with only the corresponding α_{1B} and β_1 combinations; approximately 8-fold for $\alpha_{1B-1}\alpha_{2b}\beta_{1-2}$, 10-fold for $\alpha_{1B-1}\alpha_{2b}\beta_{1-3}$, 9-fold for $\alpha_{1B-2}\alpha_{2b}\beta_{1-2}$, and 13-fold for $\alpha_{1B-2}\alpha_{2b}\beta_{1-3}$. Thus, comparison of the B_{\max} values suggests that the toxin-binding subunit, α_{1B-1} or α_{1B-2} , is more efficiently expressed and

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assembled on the cell surface when co-expressed with either the α_{2b} or the β_{1-2} or β_{1-3} subunit, and most efficiently expressed when α_{2b} and β_1 subunits are present.

3. Electrophysiology

Functional expression of $\alpha_{1B-1}\alpha_{2b}\beta_{1-2}$ and $\alpha_{1B-1}\beta_{1-2}$ subunit combinations was evaluated using the whole-cell recording technique. Transfected cells that had no contacts with surrounding cells and simple morphology were used approximately 48 hours after transfection for recording. The pipette solution was (in mM) 135 CsCl, 10 EGTA, 1 MgCl₂, 10 HEPES, and 4 mM Mg-ATP (pH 7.3, adjusted with TEA-OH). The external solution was (in mM) 15 BaCl₂, 125 Choline Cl, 1 MgCl₂, and 10 HEPES (pH 7.3, adjusted with TEA-OH). ω -CgTx GVIA (Bachem) was prepared in the external solution with 0.1% cytochrome C (Sigma) to serve as a carrier. Control experiments showed that cytochrome C had no effect on the Ba²⁺ current.

The macroscopic electrophysiological properties of Ba²⁺ currents in cells transfected with various amounts of the α_{2b} expression plasmid with the relative amounts of α_{1B-1} and β_{1-2} plasmids held constant were examined. The amplitudes and densities of the Ba²⁺ currents (15 mM BaCl₂) recorded from whole cells of these transfectants differed dramatically. The average currents from 7 to 11 cells of three types of transfections (no α_{2b} ; 2:1.8:1 [$\alpha_{1B-1}:\alpha_{2b}:\beta_{1-2}$] molar ratio; and 2:10.9:1 [$\alpha_{1B-1}:\alpha_{2b}:\beta_{1-2}$] molar ratio) were determined. The smallest currents (range: 10 to 205 pA) were recorded when α_{2b} was not included in the transfection, and the largest currents (range: 50 to 8300 pA) were recorded with the 2:10.9:1 ratio of $\alpha_{1B-1}\alpha_{2b}\beta_{1-2}$ plasmids, the ratio that resulted in near equivalent mRNA levels for each subunit transcript. When the amount of α_{2b} plasmid was adjusted to yield approximately an equal abundance of subunit mRNAs, the average peak Ba²⁺ current increased from 433 pA to 1,824 pA (4.2-fold) with a corresponding increase in average current density from 26 pA/pF to 127 pA/pF (4.9-fold). This increase is in the presence of a 2.7-fold decrease in the mass of α_{1B-1} and β_{1-2} expression plasmids in the transfections.

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In all transfections, the magnitudes of the Ba^{2+} currents did not follow a normal distribution.

To compare the subunit combinations and determine the effects of α_{2b} , the current-voltage properties of cells transfected with $\alpha_{1b-1}\beta_{1-2}$ or with $\alpha_{1b-1}\alpha_{2b}\beta_{1-2}$ in either the 2:1.8:1 ($\alpha_{1b-1}:\alpha_{2b}:\beta_{1-2}$) molar ratio or the 2:10.9:1 ($\alpha_{1b-1}:\alpha_{2b}:\beta_{1-2}$) molar ratio transfectants were examined. The extreme examples of no α_{2b} and 11.25 μg α_{2b} (2:10.9:1 molar ratio) showed no significant differences in the current voltage plot at test potentials between 0 mV and +40 mV ($p < 0.05$). The slight differences observed at either side of the peak region of the current voltage plot were likely due to normalization. The very small currents observed in the $\alpha_{1b-1}\beta_{1-2}$ transfected cells have a substantially higher component of residual leak relative to the barium current that is activated by the test pulse. When the current voltage plots are normalized, this leak is a much greater component than in the $\alpha_{1b-1}\alpha_{2b}\beta_{1-2}$ transfected cells and as a result, the current-voltage plot appears broader. This is the most likely explanation of the apparent differences in the current voltage plots, especially given the fact that the current-voltage plot for the $\alpha_{1b-1}\beta_{1-2}$ transfected cells diverge on both sides of the peak. Typically, when the voltage-dependence activation is shifted, the entire current-voltage plot is shifted, which was not observed. To qualitatively compare the kinetics of each, the average responses of test pulses from -90 mV to 10 mV were normalized and plotted. No significant differences in activation or inactivation kinetics of whole-cell Ba^{2+} currents were observed with any combination.

G. Expression of DNA encoding human neuronal calcium channel $\alpha_{1E-3}\alpha_{2B}\beta_{1-3}$ and $\alpha_{1E-1}\alpha_{2B}\beta_{1-3}$ subunits in HEK cells

Functional expression of the $\alpha_{1E-1}\alpha_{2B}\beta_{1-3}$ and $\alpha_{1E-3}\alpha_{2B}\beta_{1-3}$, as well as α_{1E-3} was evaluated using the whole cell recording technique.

1. Methods

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Recordings were performed on transiently transfected HEK 293 cells two days following the transfection, from cells that had no contacts with surrounding cells and which had simple morphology.

The internal solution used to fill pipettes for recording the barium current from the transfected recombinant calcium channels was (in mM) 135 CsCl, 10 EGTA, 1 MgCl₂, 10 HEPES, and 4 mM Mg-ATP (pH 7.4-7.5, adjusted with TEA-OH). The external solution for recording the barium current was (in mM) 15 BaCl₂, 150 Choline Cl, 1 MgCl₂, and 10 HEPES and 5 TEA-OH (pH 7.3, adjusted with TEA-OH). In experiments in which Ca²⁺ was replaced for Ba²⁺, a Laminar flow chamber was used in order to completely exchange the extracellular solution and prevent any mixing of Ba²⁺ and Ca²⁺. ω -CgTx GVIA was prepared in the external solution with 0.1% cytochrome C to serve as a carrier, the toxin was applied by pressurized puffer pipette. Series resistance was compensated 70-85% and currents were analyzed only if the voltage error from series resistance was less than 5 mV. Leak resistance and capacitance was corrected by subtracting the scaled current observed with the P/-4 protocol as implemented by pClamp (Axon Instruments).

2. Electrophysiology Results

Cells transfected with $\alpha_{1E-1}\alpha_{2b}\beta_{1-3}$ or $\alpha_{1E-3}\alpha_{2b}\beta_{1-3}$ showed strong barium currents with whole cell patch clamp recordings. Cells expressing $\alpha_{1E-3}\alpha_{2b}\beta_{1-3}$ had larger peak currents than those expressing $\alpha_{1E-1}\alpha_{2b}\beta_{1-3}$. In addition, the kinetics of activation and inactivation are clearly substantially faster in the cells expressing α_{1E} calcium channels. HEK 293 cells expressing α_{1E-3} alone have a significant degree of functional calcium channels, with properties similar to those expressing $\alpha_{1E}\alpha_{2b}\beta_{1-3}$ but with substantially smaller peak barium currents. Thus, with α_{1E} , the α_2 and β_1 subunits are not required for functional expression of α_{1E} mediated calcium channels, but do substantially increase the number of functional calcium channels.

Examination of the current voltage properties of $\alpha_{1E}\alpha_{2b}\beta_{1-3}$ expressing cells indicates that $\alpha_{1E-3}\alpha_{2b}\beta_{1-3}$ is a high-voltage

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activated calcium channel and the peak current is reached at a potential only slightly less positive than other neuronal calcium channels also expressing α_{2b} and β_1 , and α_{1B} and α_{1D} . Current voltage properties of $\alpha_{1E-1}\alpha_{2b}\beta_{1-3}$ and $\alpha_{1E-3}\alpha_{2b}\beta_{1-3}$ are statistically different from those of $\alpha_{1B-1}\alpha_{2b}\beta_{1-3}$. Current voltage curves for $\alpha_{1E-1}\alpha_{2b}\beta_{1-3}$ and $\alpha_{1E-3}\alpha_{2b}\beta_{1-3}$ peak at approximately +5mV, as does the current voltage curve for α_{1E-3} alone.

The kinetics and voltage dependence of inactivation using both prepulse (200 ms) and steady-state inactivation was examined. α_{1E} mediated calcium channels are rapidly inactivated relative to previously cloned calcium channels and other high voltage-activated calcium channels. $\alpha_{1E-3}\alpha_{2b}\beta_{1-3}$ mediated calcium channels are inactivated rapidly and are thus sensitive to relatively brief (200 ms) prepulses as well as long prepulses (>20s steady state inactivation), but recover rapidly from steady state inactivation. The kinetics of the rapid inactivation has two components, one with a time constant of approximately 25 ms and the other approximately 400 ms.

To determine whether α_{1E} mediated calcium channels have properties of low voltage activated calcium channels, the details of tail currents activated by a test pulse ranging -60 to +90 mV were measured at -60 mV. Tail currents recorded at -60 mV could be well fit by a single exponential of 150 to 300 μ s; at least an order of magnitude faster than those typically observed with low voltage-activated calcium channels.

HEK 293 cells expressing $\alpha_{1E-3}\alpha_{2b}\beta_{1-3}$ flux more current with Ba^{2+} as the charge carrier and currents carried by Ba^{2+} and Ca^{2+} have different current-voltage properties. Furthermore, the time course of inactivation is slower and the amount of prepulse inactivation less with Ca^{2+} as the charge carrier.

While the invention has been described with some specificity, modifications apparent to those with ordinary skill in the art may be made without departing from the scope of the invention. Since such modifications will be apparent to

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those of skill in the art, it is intended that this invention be limited only by the scope of the appended claims.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: THE SALK INSTITUTE BIOTECHNOLY/INDUSTRIAL ASSOCIATES
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(C) CITY: La Jolla
(D) STATE: California
(E) COUNTRY: USA
(F) POSTAL CODE (ZIP): 92037

(ii) TITLE OF INVENTION: HUMAN CALCIUM CHANNEL COMPOSITIONS AND METHODS

(iii) NUMBER OF SEQUENCES: 38

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: 08/149,097
(B) FILING DATE: 5-NOV-1993

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: 08/105,536
(B) FILING DATE: 11-AUG-1993

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7635 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 511..6996

(ix) FEATURE:

(A) NAME/KEY: 5'UTR
(B) LOCATION: 1..510

(ix) FEATURE:

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(A) NAME/KEY: 3'UTR
(B) LOCATION: 6994..7635

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GGGCGAGCGC CTCCGTCCCC GGATGTGAGC TCCGGCTGCC CGCGGTCCCC AGCCAGCGGC	60
GCGCGGGCGG CGGCGGCGGG CACCGGGCAC CGCGGCGGGC GGGCAGACGG GCGGGCATGG	120
GGGGAGCGCC GAGCGGCCCC GGCGGCCGGG CCGGCATCAC CGCGGCGTCT CTCCGCTAGA	180
GGAGGGGACA AGCCAGTTCT CCTTTGCAGC AAAAAATTAC ATGTATATAT TATTAAGATA	240
ATATATACAT TGGATTTTAT TTTTTTAAAA AGTTTATTTT GCTCCATTTT TGAAAAAGAG	300
AGAGCTTGGG TGGCGAGCGG TTTTTTTTAA AAATCAATTA TCCTTATTTT CTGTTATTTG	360
TCCCCGTCCC TCCCCACCCC CCTGCTGAAG CGAGAATAAG GGCAGGGACC GCGGCTCCTA	420
CCTCTTGGTG ATCCCCTTCC CCATTCCGCC CCCGCCCAA CGCCCAGCAC AGTGCCCTGC	480
ACACAGTAGT CGCTCAATAA ATGTTCTGTT ATG ATG ATG ATG ATG ATG ATG AAA	534
Met Met Met Met Met Met Met Met Lys	
1 5	
AAA ATG CAG CAT CAA CGG CAG CAG CAA GCG GAC CAC GCG AAC GAG GCA	582
Lys Met Gln His Gln Arg Gln Gln Gln Ala Asp His Ala Asn Glu Ala	
10 15 20	
AAC TAT GCA AGA GGC ACC AGA CTT CCT CTT TCT GGT GAA GGA CCA ACT	630
Asn Tyr Ala Arg Gly Thr Arg Leu Pro Leu Ser Gly Glu Gly Pro Thr	
25 30 35 40	
TCT CAG CCG AAT AGC TCC AAG CAA ACT GTC CTG TCT TGG CAA GCT GCA	678
Ser Gln Pro Asn Ser Ser Lys Gln Thr Val Leu Ser Trp Gln Ala Ala	
45 50 55	
ATC GAT GCT GCT AGA CAG GCC AAG GCT GCC CAA ACT ATG AGC ACC TCT	726
Ile Asp Ala Ala Arg Gln Ala Lys Ala Ala Gln Thr Met Ser Thr Ser	
60 65 70	
GCA CCC CCA CCT GTA GGA TCT CTC TCC CAA AGA AAA CGT CAG CAA TAC	774
Ala Pro Pro Pro Val Gly Ser Leu Ser Gln Arg Lys Arg Gln Gln Tyr	
75 80 85	
GCC AAG AGC AAA AAA CAG GGT AAC TCG TCC AAC AGC CGA CCT GCC CGC	822
Ala Lys Ser Lys Lys Gln Gly Asn Ser Ser Asn Ser Arg Pro Ala Arg	
90 95 100	
GCC CTT TTC TGT TTA TCA CTC AAT AAC CCC ATC CGA AGA GCC TGC ATT	870
Ala Leu Phe Cys Leu Ser Leu Asn Asn Pro Ile Arg Arg Ala Cys Ile	
105 110 115 120	
AGT ATA GTG GAA TGG AAA CCA TTT GAC ATA TTT ATA TTA TTG GCT ATT	918
Ser Ile Val Glu Trp Lys Pro Phe Asp Ile Phe Ile Leu Leu Ala Ile	
125 130 135	

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TTT	GCC	AAT	TGT	GTG	GCC	TTA	GCT	ATT	TAC	ATC	CCA	TTC	CCT	GAA	GAT	966
Phe	Ala	Asn	Cys	Val	Ala	Leu	Ala	Ile	Tyr	Ile	Pro	Phe	Pro	Glu	Asp	
			140					145					150			
GAT	TCT	AAT	TCA	ACA	AAT	CAT	AAC	TTG	GAA	AAA	GTA	GAA	TAT	GCC	TTC	1014
Asp	Ser	Asn	Ser	Thr	Asn	His	Asn	Leu	Glu	Lys	Val	Glu	Tyr	Ala	Phe	
		155					160					165				
CTG	ATT	ATT	TTT	ACA	GTC	GAG	ACA	TTT	TTG	AAG	ATT	ATA	GCG	TAT	GGA	1062
Leu	Ile	Ile	Phe	Thr	Val	Glu	Thr	Phe	Leu	Lys	Ile	Ile	Ala	Tyr	Gly	
	170					175					180					
TTA	TTG	CTA	CAT	CCT	AAT	GCT	TAT	GTT	AGG	AAT	GGA	TGG	AAT	TTA	CTG	1110
Leu	Leu	Leu	His	Pro	Asn	Ala	Tyr	Val	Arg	Asn	Gly	Trp	Asn	Leu	Leu	
185					190					195					200	
GAT	TTT	GTT	ATA	GTA	ATA	GTA	GGA	TTG	TTT	AGT	GTA	ATT	TTG	GAA	CAA	1158
Asp	Phe	Val	Ile	Val	Ile	Val	Gly	Leu	Phe	Ser	Val	Ile	Leu	Glu	Gln	
				205				210					215			
TTA	ACC	AAA	GAA	ACA	GAA	GGC	GGG	AAC	CAC	TCA	AGC	GGC	AAA	TCT	GGA	1206
Leu	Thr	Lys	Glu	Thr	Glu	Gly	Gly	Asn	His	Ser	Ser	Gly	Lys	Ser	Gly	
			220					225					230			
GGC	TTT	GAT	GTC	AAA	GCC	CTC	CGT	GCC	TTT	CGA	GTG	TTG	CGA	CCA	CTT	1254
Gly	Phe	Asp	Val	Lys	Ala	Leu	Arg	Ala	Phe	Arg	Val	Leu	Arg	Pro	Leu	
		235					240					245				
CGA	CTA	GTG	TCA	GGA	GTG	CCC	AGT	TTA	CAA	GTT	GTG	CTG	AAC	TCC	ATT	1302
Arg	Leu	Val	Ser	Gly	Val	Pro	Ser	Leu	Gln	Val	Val	Leu	Asn	Ser	Ile	
	250					255					260					
ATA	AAA	GCC	ATG	GTT	CCC	CTC	CTT	CAC	ATA	GCC	CTT	TTG	GTA	TTA	TTT	1350
Ile	Lys	Ala	Met	Val	Pro	Leu	Leu	His	Ile	Ala	Leu	Leu	Val	Leu	Phe	
265					270				275						280	
GTA	ATC	ATA	ATC	TAT	GCT	ATT	ATA	GGA	TTG	GAA	CTT	TTT	ATT	GGA	AAA	1398
Val	Ile	Ile	Ile	Tyr	Ala	Ile	Ile	Gly	Leu	Glu	Leu	Phe	Ile	Gly	Lys	
				285				290					295			
ATG	CAC	AAA	ACA	TGT	TTT	TTT	GCT	GAC	TCA	GAT	ATC	GTA	GCT	GAA	GAG	1446
Met	His	Lys	Thr	Cys	Phe	Phe	Ala	Asp	Ser	Asp	Ile	Val	Ala	Glu	Glu	
			300					305					310			
GAC	CCA	GCT	CCA	TGT	GCG	TTC	TCA	GGG	AAT	GGA	CGC	CAG	TGT	ACT	GCC	1494
Asp	Pro	Ala	Pro	Cys	Ala	Phe	Ser	Gly	Asn	Gly	Arg	Gln	Cys	Thr	Ala	
		315					320					325				
AAT	GGC	ACG	GAA	TGT	AGG	AGT	GGC	TGG	GTT	GGC	CCG	AAC	GGA	GGC	ATC	1542
Asn	Gly	Thr	Glu	Cys	Arg	Ser	Gly	Trp	Val	Gly	Pro	Asn	Gly	Gly	Ile	
	330					335					340					
ACC	AAC	TTT	GAT	AAC	TTT	GCC	TTT	GCC	ATG	CTT	ACT	GTG	TTT	CAG	TGC	1590
Thr	Asn	Phe	Asp	Asn	Phe	Ala	Phe	Ala	Met	Leu	Thr	Val	Phe	Gln	Cys	
345					350					355					360	

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ATC	ACC	ATG	GAG	GGC	TGG	ACA	GAC	GTG	CTC	TAC	TGG	ATG	AAT	GAT	GCT	1638
Ile	Thr	Met	Glu	Gly	Trp	Thr	Asp	Val	Leu	Tyr	Trp	Met	Asn	Asp	Ala	
			365						370					375		
ATG	GGA	TTT	GAA	TTG	CCC	TGG	GTG	TAT	TTT	GTC	AGT	CTC	GTC	ATC	TTT	1686
Met	Gly	Phe	Glu	Leu	Pro	Trp	Val	Tyr	Phe	Val	Ser	Leu	Val	Ile	Phe	
			380					385					390			
GGG	TCA	TTT	TTC	GTA	CTA	AAT	CTT	GTA	CTT	GGT	GTA	TTG	AGC	GGA	GAA	1734
Gly	Ser	Phe	Phe	Val	Leu	Asn	Leu	Val	Leu	Gly	Val	Leu	Ser	Gly	Glu	
		395				400						405				
TTC	TCA	AAG	GAA	AGA	GAG	AAG	GCA	AAA	GCA	CGG	GGA	GAT	TTC	CAG	AAG	1782
Phe	Ser	Lys	Glu	Arg	Glu	Lys	Ala	Lys	Ala	Arg	Gly	Asp	Phe	Gln	Lys	
	410					415					420					
CTC	CGG	GAG	AAG	CAG	CAG	CTG	GAG	GAG	GAT	CTA	AAG	GGC	TAC	TTG	GAT	1830
Leu	Arg	Glu	Lys	Gln	Gln	Leu	Glu	Glu	Asp	Leu	Lys	Gly	Tyr	Leu	Asp	
425					430					435					440	
TGG	ATC	ACC	CAA	GCT	GAG	GAC	ATC	GAT	CCG	GAG	AAT	GAG	GAA	GAA	GGA	1878
Trp	Ile	Thr	Gln	Ala	Glu	Asp	Ile	Asp	Pro	Glu	Asn	Glu	Glu	Glu	Gly	
			445					450						455		
GGA	GAG	GAA	GGC	AAA	CGA	AAT	ACT	AGC	ATG	CCC	ACC	AGC	GAG	ACT	GAG	1926
Gly	Glu	Glu	Gly	Lys	Arg	Asn	Thr	Ser	Met	Pro	Thr	Ser	Glu	Thr	Glu	
			460					465					470			
TCT	GTG	AAC	ACA	GAG	AAC	GTC	AGC	GGT	GAA	GGC	GAG	AAC	CGA	GGC	TGC	1974
Ser	Val	Asn	Thr	Glu	Asn	Val	Ser	Gly	Glu	Gly	Glu	Asn	Arg	Gly	Cys	
		475				480						485				
TGT	GGA	AGT	CTC	TGT	CAA	GCC	ATC	TCA	AAA	TCC	AAA	CTC	AGC	CGA	CGC	2022
Cys	Gly	Ser	Leu	Cys	Gln	Ala	Ile	Ser	Lys	Ser	Lys	Leu	Ser	Arg	Arg	
	490					495					500					
TGG	CGT	CGC	TGG	AAC	CGA	TTC	AAT	CGC	AGA	AGA	TGT	AGG	GCC	GCC	GTG	2070
Trp	Arg	Arg	Trp	Asn	Arg	Phe	Asn	Arg	Arg	Arg	Cys	Arg	Ala	Ala	Val	
505					510				515						520	
AAG	TCT	GTC	ACG	TTT	TAC	TGG	CTG	GTT	ATC	GTC	CTG	GTG	TTT	CTG	AAC	2118
Lys	Ser	Val	Thr	Phe	Tyr	Trp	Leu	Val	Ile	Val	Leu	Val	Phe	Leu	Asn	
			525					530					535			
ACC	TTA	ACC	ATT	TCC	TCT	GAG	CAC	TAC	AAT	CAG	CCA	GAT	TGG	TTG	ACA	2166
Thr	Leu	Thr	Ile	Ser	Ser	Glu	His	Tyr	Asn	Gln	Pro	Asp	Trp	Leu	Thr	
			540					545					550			
CAG	ATT	CAA	GAT	ATT	GCC	AAC	AAA	GTC	CTC	TTG	GCT	CTG	TTC	ACC	TGC	2214
Gln	Ile	Gln	Asp	Ile	Ala	Asn	Lys	Val	Leu	Leu	Ala	Leu	Phe	Thr	Cys	
		555				560						565				
GAG	ATG	CTG	GTA	AAA	ATG	TAC	AGC	TTG	GGC	CTC	CAA	GCA	TAT	TTC	GTC	2262
Glu	Met	Leu	Val	Lys	Met	Tyr	Ser	Leu	Gly	Leu	Gln	Ala	Tyr	Phe	Val	
	570					575					580					

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TCT	CTT	TTC	AAC	CGG	TTT	GAT	TGC	TTC	GTG	GTG	TGT	GGT	GGA	ATC	ACT	2310
Ser	Leu	Phe	Asn	Arg	Phe	Asp	Cys	Phe	Val	Val	Cys	Gly	Gly	Ile	Thr	
585					590					595					600	
GAG	ACG	ATC	TTG	GTG	GAA	CTG	GAA	ATC	ATG	TCT	CCC	CTG	GGG	ATC	TCT	2358
Glu	Thr	Ile	Leu	Val	Glu	Leu	Glu	Ile	Met	Ser	Pro	Leu	Gly	Ile	Ser	
				605					610					615		
GTG	TTT	CGG	TGT	GTG	CGC	CTC	TTA	AGA	ATC	TTC	AAA	GTG	ACC	AGG	CAC	2406
Val	Phe	Arg	Cys	Val	Arg	Leu	Leu	Arg	Ile	Phe	Lys	Val	Thr	Arg	His	
			620					625					630			
TGG	ACT	TCC	CTG	AGC	AAC	TTA	GTG	GCA	TCC	TTA	TTA	AAC	TCC	ATG	AAG	2454
Trp	Thr	Ser	Leu	Ser	Asn	Leu	Val	Ala	Ser	Leu	Leu	Asn	Ser	Met	Lys	
		635					640					645				
TCC	ATC	GCT	TCG	CTG	TTG	CTT	CTG	CTT	TTT	CTC	TTC	ATT	ATC	ATC	TTT	2502
Ser	Ile	Ala	Ser	Leu	Leu	Leu	Leu	Leu	Phe	Leu	Phe	Ile	Ile	Ile	Phe	
	650					655					660					
TCC	TTG	CTT	GGG	ATG	CAG	CTG	TTT	GGC	GGC	AAG	TTT	AAT	TTT	GAT	GAA	2550
Ser	Leu	Leu	Gly	Met	Gln	Leu	Phe	Gly	Gly	Lys	Phe	Asn	Phe	Asp	Glu	
665					670					675					680	
ACG	CAA	ACC	AAG	CGG	AGC	ACC	TTT	GAC	AAT	TTC	CCT	CAA	GCA	CTT	CTC	2598
Thr	Gln	Thr	Lys		Ser	Thr	Phe	Asp	Asn	Phe	Pro	Gln	Ala	Leu	Leu	
			685						690					695		
ACA	GTG	TTC	CAG	ATC	CTG	ACA	GGC	GAA	GAC	TGG	AAT	GCT	GTG	ATG	TAC	2646
Thr	Val	Phe	Gln	Ile	Leu	Thr	Gly	Glu	Asp	Trp	Asn	Ala	Val	Met	Tyr	
			700					705					710			
GAT	GGC	ATC	ATG	GCT	TAC	GGG	GGC	CCA	TCC	TCT	TCA	GGA	ATG	ATC	GTC	2694
Asp	Gly	Ile	Met	Ala	Tyr	Gly	Gly	Pro	Ser	Ser	Ser	Gly	Met	Ile	Val	
		715				720						725				
TGC	ATC	TAC	TTC	ATC	ATC	CTC	TTC	ATT	TGT	GGT	AAC	TAT	ATT	CTA	CTG	2742
Cys	Ile	Tyr	Phe	Ile	Ile	Leu	Phe	Ile	Cys	Gly	Asn	Tyr	Ile	Leu	Leu	
	730					735					740					
AAT	GTC	TTC	TTG	GCC	ATC	GCT	GTA	GAC	AAT	TTG	GCT	GAT	GCT	GAA	AGT	2790
Asn	Val	Phe	Leu	Ala	Ile	Ala	Val	Asp	Asn	Leu	Ala	Asp	Ala	Glu	Ser	
745					750				755					760		
CTG	AAC	ACT	GCT	CAG	AAA	GAA	GAA	GCG	GAA	GAA	AAG	GAG	AGG	AAA	AAG	2838
Leu	Asn	Thr	Ala	Gln	Lys	Glu	Glu	Ala	Glu	Glu	Lys	Glu	Arg	Lys	Lys	
				765					770					775		
ATT	GCC	AGA	AAA	GAG	AGC	CTA	GAA	AAT	AAA	AAG	AAC	AAC	AAA	CCA	GAA	2886
Ile	Ala	Arg	Lys	Glu	Ser	Leu	Glu	Asn	Lys	Lys	Asn	Asn	Lys	Pro	Glu	
			780					785					790			
GTC	AAC	CAG	ATA	GCC	AAC	AGT	GAC	AAC	AAG	GTT	ACA	ATT	GAT	GAC	TAT	2934
Val	Asn	Gln	Ile	Ala	Asn	Ser	Asp	Asn	Lys	Val	Thr	Ile	Asp	Asp	Tyr	
		795					800						805			

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AGA Arg	GAA Glu	GAG Glu	GAT Asp	GAA Glu	GAC Asp	AAG Lys	GAC Asp	CCC Pro	TAT Tyr	CCG Pro	CCT Pro	TGC Cys	GAT Asp	GTG Val	CCA Pro	2982
	810					815					820					
GTA Val	GGG Gly	GAA Glu	GAG Glu	GAA Glu	GAG Glu	GAA Glu	GAG Glu	GAG Glu	GAG Glu	GAT Asp	GAA Glu	CCT Pro	GAG Glu	GTT Val	CCT Pro	3030
	825					830				835					840	
GCC Ala	GGA Gly	CCC Pro	CGT Arg	CCT Pro	CGA Arg	AGG Arg	ATC Ile	TCG Ser	GAG Glu	TTG Leu	AAC Asn	ATG Met	AAG Lys	GAA Glu	AAA Lys	3078
				845					850					855		
ATT Ile	GCC Ala	CCC Pro	ATC Ile	CCT Pro	GAA Glu	GGG Gly	AGC Ser	GCT Ala	TTC Phe	TTC Phe	ATT Ile	CTT Leu	AGC Ser	AAG Lys	ACC Thr	3126
			860					865					870			
AAC Asn	CCG Pro	ATC Ile	CGC Arg	GTA Val	GGC Gly	TGC Cys	CAC His	AAG Lys	CTC Leu	ATC Ile	AAC Asn	CAC His	CAC His	ATC Ile	TTC Phe	3174
		875					880					885				
ACC Thr	AAC Asn	CTC Leu	ATC Ile	CTT Leu	GTC Val	TTC Phe	ATC Ile	ATG Met	CTG Leu	AGC Ser	AGT Ser	GCT Ala	GCC Ala	CTG Leu	GCC Ala	3222
	890					895					900					
GCA Ala	GAG Glu	GAC Asp	CCC Pro	ATC Ile	CGC Arg	AGC Ser	CAC His	TCC Ser	TTC Phe	CGG Arg	AAC Asn	ACG Thr	ATA Ile	CTG Leu	GGT Gly	3270
	905				910					915					920	
TAC Tyr	TTT Phe	GAC Asp	TAT Tyr	GCC Ala	TTC Phe	ACA Thr	GCC Ala	ATC Ile	TTT Phe	ACT Thr	GTT Val	GAG Glu	ATC Ile	CTG Leu	TTG Leu	3318
				925					930					935		
AAG Lys	ATG Met	ACA Thr	ACT Thr	TTT Phe	GGA Gly	GCT Ala	TTC Phe	CTC Leu	CAC His	AAA Lys	GGG Gly	GCC Ala	TTC Phe	TGC Cys	AGG Arg	3366
			940					945					950			
AAC Asn	TAC Tyr	TTC Phe	AAT Asn	TTG Leu	CTG Leu	GAT Asp	ATG Met	CTG Leu	GTG Val	GTT Val	GGG Gly	GTG Val	TCT Ser	CTG Leu	GTG Val	3414
		955				960					965					
TCA Ser	TTT Phe	GGG Gly	ATT Ile	CAA Gln	TCC Ser	AGT Ser	GCC Ala	ATC Ile	TCC Ser	GTT Val	GTG Val	AAG Lys	ATT Ile	CTG Leu	AGG Arg	3462
	970					975					980					
GTC Val	TTA Leu	AGG Arg	GTC Val	CTG Leu	CGT Arg	CCC Pro	CTC Leu	AGG Arg	GCC Ala	ATC Ile	AAC Asn	AGA Arg	GCA Ala	AAA Lys	GGA Gly	3510
	985				990				995						1000	
CTT Leu	AAG Lys	CAC His	GTG Val	GTC Val	CAG Gln	TGC Cys	GTC Val	TTC Phe	GTG Val	GCC Ala	ATC Ile	CGG Arg	ACC Thr	ATC Ile	GGC Gly	3558
				1005					1010					1015		
AAC Asn	ATC Ile	ATG Met	ATC Ile	GTC Val	ACC Thr	ACC Thr	CTC Leu	CTG Leu	CAG Gln	TTC Phe	ATG Met	TTT Phe	GCC Ala	TGT Cys	ATC Ile	3606
			1020					1025					1030			

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GGG GTC CAG TTG TTC AAG GGG AAG TTC TAT CGC TGT ACG GAT GAA GCC	3654
Gly Val Gln Leu Phe Lys Gly Lys Phe Tyr Arg Cys Thr Asp Glu Ala	
1035 1040 1045	
AAA AGT AAC CCT GAA GAA TGC AGG GGA CTT TTC ATC CTC TAC AAG GAT	3702
Lys Ser Asn Pro Glu Glu Cys Arg Gly Leu Phe Ile Leu Tyr Lys Asp	
1050 1055 1060	
GGG GAT GTT GAC AGT CCT GTG GTC CGT GAA CGG ATC TGG CAA AAC AGT	3750
Gly Asp Val Asp Ser Pro Val Val Arg Glu Arg Ile Trp Gln Asn Ser	
1065 1070 1075 1080	
GAT TTC AAC TTC GAC AAC GTC CTC TCT GCT ATG ATG GCG CTC TTC ACA	3798
Asp Phe Asn Phe Asp Asn Val Leu Ser Ala Met Met Ala Leu Phe Thr	
1085 1090 1095	
GTC TCC ACG TTT GAG GGC TGG CCT GCG TTG CTG TAT AAA GCC ATC GAC	3846
Val Ser Thr Phe Glu Gly Trp Pro Ala Leu Leu Tyr Lys Ala Ile Asp	
1100 1105 1110	
TCG AAT GGA GAG AAC ATC GGC CCA ATC TAC AAC CAC CGC GTG GAG ATC	3894
Ser Asn Gly Glu Asn Ile Gly Pro Ile Tyr Asn His Arg Val Glu Ile	
1115 1120 1125	
TCC ATC TTC TTC ATC ATC TAC ATC ATC ATT GTA GCT TTC TTC ATG ATG	3942
Ser Ile Phe Phe Ile Ile Tyr Ile Ile Ile Val Ala Phe Phe Met Met	
1130 1135 1140	
AAC ATC TTT GTG GGC TTT GTC ATC GTT ACA TTT CAG GAA CAA GGA GAA	3990
Asn Ile Phe Val Gly Phe Val Ile Val Thr Phe Gln Glu Gln Gly Glu	
1145 1150 1155 1160	
AAA GAG TAT AAG AAC TGT GAG CTG GAC AAA AAT CAG CGT CAG TGT GTT	4038
Lys Glu Tyr Lys Asn Cys Glu Leu Asp Lys Asn Gln Arg Gln Cys Val	
1165 1170 1175	
GAA TAC GCC TTG AAA GCA CGT CCC TTG CGG AGA TAC ATC CCC AAA AAC	4086
Glu Tyr Ala Leu Lys Ala Arg Pro Leu Arg Arg Tyr Ile Pro Lys Asn	
1180 1185 1190	
CCC TAC CAG TAC AAG TTC TGG TAC GTG GTG AAC TCT TCG CCT TTC GAA	4134
Pro Tyr Gln Tyr Lys Phe Trp Tyr Val Val Asn Ser Ser Pro Phe Glu	
1195 1200 1205	
TAC ATG ATG TTT GTC CTC ATC ATG CTC AAC ACA CTC TGC TTG GCC ATG	4182
Tyr Met Met Phe Val Leu Ile Met Leu Asn Thr Leu Cys Leu Ala Met	
1210 1215 1220	
CAG CAC TAC GAG CAG TCC AAG ATG TTC AAT GAT GCC ATG GAC ATT CTG	4230
Gln His Tyr Glu Gln Ser Lys Met Phe Asn Asp Ala Met Asp Ile Leu	
1225 1230 1235 1240	
AAC ATG GTC TTC ACC GGG GTG TTC ACC GTC GAG ATG GTT TTG AAA GTC	4278
Asn Met Val Phe Thr Gly Val Phe Thr Val Glu Met Val Leu Lys Val	
1245 1250 1255	

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ATC GCA TTT AAG CCT AAG GGG TAT TTT AGT GAC GCC TGG AAC ACG TTT Ile Ala Phe Lys Pro Lys Gly Tyr Phe Ser Asp Ala Trp Asn Thr Phe 1260 1265 1270	4326
GAC TCC CTC ATC GTA ATC GGC AGC ATT ATA GAC GTG GCC CTC AGC GAA Asp Ser Leu Ile Val Ile Gly Ser Ile Ile Asp Val Ala Leu Ser Glu 1275 1280 1285	4374
GCA GAC CCA ACT GAA AGT GAA AAT GTC CCT GTC CCA ACT GCT ACA CCT Ala Asp Pro Thr Glu Ser Glu Asn Val Pro Val Thr Ala Thr Pro 1290 1295 1300	4422
GGG AAC TCT GAA GAG AGC AAT AGA ATC TCC ATC ACC TTT TTC CGT CTT Gly Asn Ser Glu Glu Ser Asn Arg Ile Ser Ile Thr Phe Phe Arg Leu 1305 1310 1315 1320	4470
TTC CGA GTG ATG CGA TTG GTG AAG CTT CTC AGC AGG GGG GAA GGC ATC Phe Arg Val Met Arg Leu Val Lys Leu Leu Ser Arg Gly Glu Gly Ile 1325 1330 1335	4518
CGG ACA TTG CTG TGG ACT TTT ATT AAG TTC TTT CAG GCG CTC CCG TAT Arg Thr Leu Leu Trp Thr Phe Ile Lys Phe Phe Gln Ala Leu Pro Tyr 1340 1345 1350	4566
GTG GCC CTC CTC ATA GCC ATG CTG TTC TTC ATC TAT GCG GTC ATT GGC Val Ala Leu Leu Ile Ala Met Leu Phe Phe Ile Tyr Ala Val Ile Gly 1355 1360 1365	4614
ATG CAG ATG TTT GGG AAA GTT GCC ATG AGA GAT AAC AAC CAG ATC AAT Met Gln Met Phe Gly Lys Val Ala Met Arg Asp Asn Asn Gln Ile Asn 1370 1375 1380	4662
AGG AAC AAT AAC TTC CAG ACG TTT CCC CAG GCG GTG CTG CTG CTC TTC Arg Asn Asn Asn Phe Gln Thr Phe Pro Gln Ala Val Leu Leu Leu Phe 1385 1390 1395 1400	4710
AGG TGT GCA ACA GGT GAG GCC TGG CAG GAG ATC ATG CTG GCC TGT CTC Arg Cys Ala Thr Gly Glu Ala Trp Gln Glu Ile Met Leu Ala Cys Leu 1405 1410 1415	4758
CCA GGG AAG CTC TGT GAC CCT GAG TCA GAT TAC AAC CCC GGG GAG GAG Pro Gly Lys Leu Cys Asp Pro Glu Ser Asp Tyr Asn Pro Gly Glu Glu 1420 1425 1430	4806
CAT ACA TGT GGG AGC AAC TTT GCC ATT GTC TAT TTC ATC AGT TTT TAC His Thr Cys Gly Ser Asn Phe Ala Ile Val Tyr Phe Ile Ser Phe Tyr 1435 1440 1445	4854
ATG CTC TGT GCA TTT CTG ATC ATC AAT CTG TTT GTG GCT GTC ATC ATG Met Leu Cys Ala Phe Leu Ile Ile Asn Leu Phe Val Ala Val Ile Met 1450 1455 1460	4902
GAT AAT TTC GAC TAT CTG ACC CGG GAC TGG TCT ATT TTG GGG CCT CAC Asp Asn Phe Asp Tyr Leu Thr Arg Asp Trp Ser Ile Leu Gly Pro His 1465 1470 1475 1480	4950

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CAT TTA GAT GAA TTC AAA AGA ATA TGG TCA GAA TAT GAC CCT GAG GCA	4998
His Leu Asp Glu Phe Lys Arg Ile Trp Ser Glu Tyr Asp Pro Glu Ala	
1485 1490 1495	
AAG GGA AGG ATA AAA CAC CTT GAT GTG GTC ACT CTG CTT CGA CGC ATC	5046
Lys Gly Arg Ile Lys His Leu Asp Val Val Thr Leu Leu Arg Arg Ile	
1500 1505 1510	
CAG CCT CCC CTG GGG TTT GGG AAG TTA TGT CCA CAC AGG GTA GCG TGC	5094
Gln Pro Pro Leu Gly Phe Gly Lys Leu Cys Pro His Arg Val Ala Cys	
1515 1520 1525	
AAG AGA TTA GTT GCC ATG AAC ATG CCT CTC AAC AGT GAC GGG ACA GTC	5142
Lys Arg Leu Val Ala Met Asn Met Pro Leu Asn Ser Asp Gly Thr Val	
1530 1535 1540	
ATG TTT AAT GCA ACC CTG TTT GCT TTG GTT CGA ACG GCT CTT AAG ATC	5190
Met Phe Asn Ala Thr Leu Phe Ala Leu Val Arg Thr Ala Leu Lys Ile	
1545 1550 1555 1560	
AAG ACC GAA GGG AAC CTG GAG CAA GCT AAT GAA GAA CTT CGG GCT GTG	5238
Lys Thr Glu Gly Asn Leu Glu Gln Ala Asn Glu Glu Leu Arg Ala Val	
1565 1570 1575	
ATA AAG AAA ATT TGG AAG AAA ACC AGC ATG AAA TTA CTT GAC CAA GTT	5286
Ile Lys Lys Ile Trp Lys Lys Thr Ser Met Lys Leu Leu Asp Gln Val	
1580 1585 1590	
GTC CCT CCA GCT GGT GAT GAT GAG GTA ACC GTG GGG AAG TTC TAT GCC	5334
Val Pro Pro Ala Gly Asp Asp Glu Val Thr Val Gly Lys Phe Tyr Ala	
1595 1600 1605	
ACT TTC CTG ATA CAG GAC TAC TTT AGG AAA TTC AAG AAA CGG AAA GAA	5382
Thr Phe Leu Ile Gln Asp Tyr Phe Arg Lys Phe Lys Lys Arg Lys Glu	
1610 1615 1620	
CAA GGA CTG GTG GGA AAG TAC CCT GCG AAG AAC ACC ACA ATT GCC CTA	5430
Gln Gly Leu Val Gly Lys Tyr Pro Ala Lys Asn Thr Thr Ile Ala Leu	
1625 1630 1635 1640	
CAG GCG GGA TTA AGG ACA CTG CAT GAC ATT GGG CCA GAA ATC CGG CGT	5478
Gln Ala Gly Leu Arg Thr Leu His Asp Ile Gly Pro Glu Ile Arg Arg	
1645 1650 1655	
GCT ATA TCG TGT GAT TTG CAA GAT GAC GAG CCT GAG GAA ACA AAA CGA	5526
Ala Ile Ser Cys Asp Leu Gln Asp Asp Glu Pro Glu Glu Thr Lys Arg	
1660 1665 1670	
GAA GAA GAA GAT GAT GTG TTC AAA AGA AAT GGT GCC CTG CTT GGA AAC	5574
Glu Glu Glu Asp Asp Val Phe Lys Arg Asn Gly Ala Leu Leu Gly Asn	
1675 1680 1685	
CAT GTC AAT CAT GTT AAT AGT GAT AGG AGA GAT TCC CTT CAG CAG ACC	5622
His Val Asn His Val Asn Ser Asp Arg Arg Asp Ser Leu Gln Gln Thr	
1690 1695 1700	

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AAT ACC ACC CAC CGT CCC CTG CAT GTC CAA AGG CCT TCA ATT CCA CCT Asn Thr Thr His Arg Pro Leu His Val Gln Arg Pro Ser Ile Pro Pro 1705 1710 1715 1720	5670
GCA AGT GAT ACT GAG AAA CCG CTG TTT CCT CCA GCA GGA AAT TCG GTG Ala Ser Asp Thr Glu Lys Pro Leu Phe Pro Pro Ala Gly Asn Ser Val 1725 1730 1735	5718
TGT CAT AAC CAT CAT AAC CAT AAT TCC ATA GGA AAG CAA GTT CCC ACC Cys His Asn His His Asn His Asn Ser Ile Gly Lys Gln Val Pro Thr 1740 1745 1750	5766
TCA ACA AAT GCC AAT CTC AAT AAT GCC AAT ATG TCC AAA GCT GCC CAT Ser Thr Asn Ala Asn Leu Asn Asn Ala Asn Met Ser Lys Ala Ala His 1755 1760 1765	5814
GGA AAG CGG CCC AGC ATT GGG AAC CTT GAG CAT GTG TCT GAA AAT GGG Gly Lys Arg Pro Ser Ile Gly Asn Leu Glu His Val Ser Glu Asn Gly 1770 1775 1780	5862
CAT CAT TCT TCC CAC AAG CAT GAC CGG GAG CCT CAG AGA AGG TCC AGT His His Ser Ser His Lys His Asp Arg Glu Pro Gln Arg Arg Ser Ser 1785 1790 1795 1800	5910
GTG AAA AGA ACC CGC TAT TAT GAA ACT TAC ATT AGG TCC GAC TCA GGA Val Lys Arg Thr Arg Tyr Tyr Glu Thr Tyr Ile Arg Ser Asp Ser Gly 1805 1810 1815	5958
GAT GAA CAG CTC CCA ACT ATT TGC CGG GAA GAC CCA GAG ATA CAT GGC Asp Glu Gln Leu Pro Thr Ile Cys Arg Glu Asp Pro Glu Ile His Gly 1820 1825 1830	6006
TAT TTC AGG GAC CCC CAC TGC TTG GGG GAG CAG GAG TAT TTC AGT AGT Tyr Phe Arg Asp Pro His Cys Leu Gly Glu Gln Glu Tyr Phe Ser Ser 1835 1840 1845	6054
GAG GAA TGC TAC GAG GAT GAC AGC TCG CCC ACC TGG AGC AGG CAA AAC Glu Glu Cys Tyr Glu Asp Asp Ser Ser Pro Thr Trp Ser Arg Gln Asn 1850 1855 1860	6102
TAT GGC TAC TAC AGC AGA TAC CCA GGC AGA AAC ATC GAC TCT GAG AGG Tyr Gly Tyr Tyr Ser Arg Tyr Pro Gly Arg Asn Ile Asp Ser Glu Arg 1865 1870 1875 1880	6150
CCC CGA GGC TAC CAT CAT CCC CAA GGA TTC TTG GAG GAC GAT GAC TCG Pro Arg Gly Tyr His His Pro Gln Gly Phe Leu Glu Asp Asp Asp Ser 1885 1890 1895	6198
CCC GTT TGC TAT GAT TCA CGG AGA TCT CCA AGG AGA CGC CTA CTA CCT Pro Val Cys Tyr Asp Ser Arg Arg Ser Pro Arg Arg Arg Leu Leu Pro 1900 1905 1910	6246
CCC ACC CCA GCA TCC CAC CGG AGA TCC TCC TTC AAC TTT GAG TGC CTG Pro Thr Pro Ala Ser His Arg Arg Ser Ser Phe Asn Phe Glu Cys Leu 1915 1920 1925	6294

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CGC	CGG	CAG	AGC	AGC	CAG	GAA	GAG	GTC	CCG	TCG	TCT	CCC	ATC	TTC	CCC	6342
Arg	Arg	Gln	Ser	Ser	Gln	Glu	Glu	Val	Pro	Ser	Ser	Pro	Ile	Phe	Pro	
1930						1935					1940					
CAT	CGC	ACG	GCC	CTG	CCT	CTG	CAT	CTA	ATG	CAG	CAA	CAG	ATC	ATG	GCA	6390
His	Arg	Thr	Ala	Leu	Pro	Leu	His	Leu	Met	Gln	Gln	Gln	Ile	Met	Ala	
1945					1950					1955					1960	
GTT	GCC	GGC	CTA	GAT	TCA	AGT	AAA	GCC	CAG	AAG	TAC	TCA	CCG	AGT	CAC	6438
Val	Ala	Gly	Leu	Asp	Ser	Ser	Lys	Ala	Gln	Lys	Tyr	Ser	Pro	Ser	His	
				1965					1970					1975		
TCG	ACC	CGG	TCG	TGG	GCC	ACC	CCT	CCA	GCA	ACC	CCT	CCC	TAC	CGG	GAC	6486
Ser	Thr	Arg	Ser	Trp	Ala	Thr	Pro	Pro	Ala	Thr	Pro	Pro	Tyr	Arg	Asp	
			1980					1985					1990			
TGG	ACA	CCG	TGC	TAC	ACC	CCC	CTG	ATC	CAA	GTG	GAG	CAG	TCA	GAG	GCC	6534
Trp	Thr	Pro	Cys	Tyr	Thr	Pro	Leu	Ile	Gln	Val	Glu	Gln	Ser	Glu	Ala	
		1995					2000					2005				
CTG	GAC	CAG	GTG	AAC	GGC	AGC	CTG	CCG	TCC	CTG	CAC	CGC	AGC	TCC	TGG	6582
Leu	Asp	Gln	Val	Asn	Gly	Ser	Leu	Pro	Ser	Leu	His	Arg	Ser	Ser	Trp	
2010						2015					2020					
TAC	ACA	GAC	GAG	CCC	GAC	ATC	TCC	TAC	CGG	ACT	TTC	ACA	CCA	GCC	AGC	6630
Tyr	Thr	Asp	Glu	Pro	Asp	Ile	Ser	Tyr	Arg	Thr	Phe	Thr	Pro	Ala	Ser	
2025					2030					2035					2040	
CTG	ACT	GTC	CCC	AGC	AGC	TTC	CGG	AAC	AAA	AAC	AGC	GAC	AAG	CAG	AGG	6678
Leu	Thr	Val	Pro	Ser	Ser	Phe	Arg	Asn	Lys	Asn	Ser	Asp	Lys	Gln	Arg	
			2045					2050						2055		
AGT	GCG	GAC	AGC	TTG	GTG	GAG	GCA	GTC	CTG	ATA	TCC	GAA	GGC	TTG	GGA	6726
Ser	Ala	Asp	Ser	Leu	Val	Glu	Ala	Val	Leu	Ile	Ser	Glu	Gly	Leu	Gly	
			2060					2065					2070			
CGC	TAT	GCA	AGG	GAC	CCA	AAA	TTT	GTG	TCA	GCA	ACA	AAA	CAC	GAA	ATC	6774
Arg	Tyr	Ala	Arg	Asp	Pro	Lys	Phe	Val	Ser	Ala	Thr	Lys	His	Glu	Ile	
		2075					2080					2085				
GCT	GAT	GCC	TGT	GAC	CTC	ACC	ATC	GAC	GAG	ATG	GAG	AGT	GCA	GCC	AGC	6822
Ala	Asp	Ala	Cys	Asp	Leu	Thr	Ile	Asp	Glu	Met	Glu	Ser	Ala	Ala	Ser	
	2090					2095					2100					
ACC	CTG	CTT	AAT	GGG	AAC	GTG	CGT	CCC	CGA	GCC	AAC	GGG	GAT	GTG	GGC	6870
Thr	Leu	Leu	Asn	Gly	Asn	Val	Arg	Pro	Arg	Ala	Asn	Gly	Asp	Val	Gly	
2105					2110					2115				2120		
CCC	CTC	TCA	CAC	CGG	CAG	GAC	TAT	GAG	CTA	CAG	GAC	TTT	GGT	CCT	GGC	6918
Pro	Leu	Ser	His	Arg	Gln	Asp	Tyr	Glu	Leu	Gln	Asp	Phe	Gly	Pro	Gly	
			2125					2130						2135		
TAC	AGC	GAC	GAA	GAG	CCA	GAC	CCT	GGG	AGG	GAT	GAG	GAG	GAC	CTG	GCG	6966
Tyr	Ser	Asp	Glu	Glu	Pro	Asp	Pro	Gly	Arg	Asp	Glu	Glu	Asp	Leu	Ala	
			2140					2145					2150			

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GAT GAA ATG ATA TGC ATC ACC ACC TTG TAGCCCCCAG CGAGGGGCAG 7013
 Asp Glu Met Ile Cys Ile Thr Thr Leu
 2155 2160

ACTGGCTCTG GCCTCAGGTG GGGCGCAGGA GAGCCAGGGG AAAAGTGCCT CATAGTTAGG 7073

AAAGTTTAGG CACTAGTTGG GAGTAATATT CAATTAATTA GACTTTTGTA TAAGAGATGT 7133

CATGCCTCAA GAAAGCCATA AACCTGGTAG GAACAGGTCC CAAGCGGTTG AGCCTGGCAG 7193

AGTACCATGC GCTCGGCCCC AGCTGCAGGA AACAGCAGGC CCCGCCCTCT CACAGAGGAT 7253

GGGTGAGGAG GCCAGACCTG CCCTGCCCCA TTGTCCAGAT GGGCACTGCT GTGGAGTCTG 7313

CTTCTCCCAT GTACCAGGGC ACCAGGCCCA CCCAACTGAA GGCATGGCGG CGGGGTGCAG 7373

GGGAAAGTTA AAGGTGATGA CGATCATCAC ACCTGTGTCTG TTACCTCAGC CATCGGTCTA 7433

GCATATCAGT CACTGGGCCC AACATATCCA TTTTAAACC CTTTCCCCCA AATACACTGC 7493

GTCCTGGTTC CTGTTTAGCT GTTCTGAAAT ACGGTGTGTA AGTAAGTCAG AACCCAGCTA 7553

CCAGTGATTA TTGCGAGGGC AATGGGACCT CATAAATAAG GTTTTCTGTG ATGTGACGCC 7613

AGTTTACATA AGAGAATATC AC 7635

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 104 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..102

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 1..104
- (D) OTHER INFORMATION: /note= "A 104-nucleotide alternative exon of alpha-1D."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

GTA AAT GAT GCG ATA GGA TGG GAA TGG CCA TGG GTG TAT TTT GTT AGT 48
 Val Asn Asp Ala Ile Gly Trp Glu Trp Pro Trp Val Tyr Phe Val Ser
 1 5 10 15

CTG ATC ATC CTT GGC TCA TTT TTC GTC CTT AAC CTG GTT CTT GGT GTC 96
 Leu Ile Ile Leu Gly Ser Phe Phe Val Leu Asn Leu Val Leu Gly Val
 20 25 30

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CTT AGT GG
Leu Ser

104

(2) INFORMATION FOR SEQ ID NO:3:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 6575 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 1..6492

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ATG GTC AAT GAG AAT ACG AGG ATG TAC ATT CCA GAG GAA AAC CAC CAA	48
Met Val Asn Glu Asn Thr Arg Met Tyr Ile Pro Glu Glu Asn His Gln	
1 5 10 15	
GGT TCC AAC TAT GGG AGC CCA CGC CCC GCC CAT GCC AAC ATG AAT GCC	96
Gly Ser Asn Tyr Gly Ser Pro Arg Pro Ala His Ala Asn Met Asn Ala	
20 25 30	
AAT GCG GCA GCG GGG CTG GCC CCT GAG CAC ATC CCC ACC CCG GGG GCT	144
Asn Ala Ala Ala Gly Leu Ala Pro Glu His Ile Pro Thr Pro Gly Ala	
35 40 45	
GCC CTG TCG TGG CAG GCG GCC ATC GAC GCA GCC CGG CAG GCT AAG CTG	192
Ala Leu Ser Trp Gln Ala Ala Ile Asp Ala Ala Arg Gln Ala Lys Leu	
50 55 60	
ATG GGC AGC GCT GGC AAT GCG ACC ATC TCC ACA GTC AGC TCC ACG CAG	240
Met Gly Ser Ala Gly Asn Ala Thr Ile Ser Thr Val Ser Ser Thr Gln	
65 70 75 80	
CGG AAG CGC CAG CAA TAT GGG AAA CCC AAG AAG CAG GGC AGC ACC ACG	288
Arg Lys Arg Gln Gln Tyr Gly Lys Pro Lys Lys Gln Gly Ser Thr Thr	
85 90 95	
GCC ACA CGC CCG CCC CGA GCC CTG CTC TGC CTG ACC CTG AAG AAC CCC	336
Ala Thr Arg Pro Pro Arg Ala Leu Leu Cys Leu Thr Leu Lys Asn Pro	
100 105 110	
ATC CGG AGG GCC TGC ATC AGC ATT GTC GAA TGG AAA CCA TTT GAA ATA	384
Ile Arg Arg Ala Cys Ile Ser Ile Val Glu Trp Lys Pro Phe Glu Ile	
115 120 125	
ATT ATT TTA CTG ACT ATT TTT GCC AAT TGT GTG GCC TTA GCG ATC TAT	432
Ile Ile Leu Leu Thr Ile Phe Ala Asn Cys Val Ala Leu Ala Ile Tyr	
130 135 140	
ATT CCC TTT CCA GAA GAT GAT TCC AAC GCC ACC AAT TCC AAC CTG GAA	480

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Ile 145	Pro	Phe	Pro	Glu	Asp 150	Asp	Ser	Asn	Ala	Thr 155	Asn	Ser	Asn	Leu	Glu 160	
CGA	GTG	GAA	TAT	CTC	TTT	CTC	ATA	ATT	TTT	ACG	GTG	GAA	GCG	TTT	TTA	528
Arg	Val	Glu	Tyr	Leu	Phe	Leu	Ile	Ile	Phe	Thr	Val	Glu	Ala	Phe	Leu	
				165					170					175		
AAA	GTA	ATC	GCC	TAT	GGA	CTC	CTC	TTT	CAC	CCC	AAT	GCC	TAC	CTC	CGC	576
Lys	Val	Ile	Ala	Tyr	Gly	Leu	Leu	Phe	His	Pro	Asn	Ala	Tyr	Leu	Arg	
			180					185					190			
AAC	GGC	TGG	AAC	CTA	CTA	GAT	TTT	ATA	ATT	GTG	GTT	GTG	GGG	CTT	TTT	624
Asn	Gly	Trp	Asn	Leu	Leu	Asp	Phe	Ile	Ile	Val	Val	Val	Gly	Leu	Phe	
		195					200					205				
AGT	GCA	ATT	TTA	GAA	CAA	GCA	ACC	AAA	GCA	GAT	GGG	GCA	AAC	GCT	CTC	672
Ser	Ala	Ile	Leu	Glu	Gln	Ala	Thr	Lys	Ala	Asp	Gly	Ala	Asn	Ala	Leu	
	210					215					220					
GGA	GGG	AAA	GGG	GCC	GGA	TTT	GAT	GTG	AAG	GCG	CTG	AGG	GCC	TTC	CGC	720
Gly	Gly	Lys	Gly	Ala	Gly	Phe	Asp	Val	Lys	Ala	Leu	Arg	Ala	Phe	Arg	
225					230					235					240	
GTG	CTG	CGC	CCC	CTG	CGG	CTG	GTG	TCC	GGA	GTC	CCA	AGT	CTC	CAG	GTG	768
Val	Leu	Arg	Pro	Leu	Arg	Leu	Val	Ser	Gly	Val	Pro	Ser	Leu	Gln	Val	
				245					250					255		
GTC	CTG	AAT	TCC	ATC	ATC	AAG	GCC	ATG	GTC	CCC	CTG	CTG	CAC	ATC	GCC	816
Val	Leu	Asn	Ser	Ile	Ile	Lys	Ala	Met	Val	Pro	Leu	Leu	His	Ile	Ala	
			260					265					270			
CTG	CTT	GTG	CTG	TTT	GTC	ATC	ATC	ATC	TAC	GCC	ATC	ATC	GGC	TTG	GAG	864
Leu	Leu	Val	Leu	Phe	Val	Ile	Ile	Ile	Tyr	Ala	Ile	Ile	Gly	Leu	Glu	
		275					280					285				
CTC	TTC	ATG	GGG	AAG	ATG	CAC	AAG	ACC	TGC	TAC	AAC	CAG	GAG	GGC	ATA	912
Leu	Phe	Met	Gly	Lys	Met	His	Lys	Thr	Cys	Tyr	Asn	Gln	Glu	Gly	Ile	
	290					295					300					
GCA	GAT	GTT	CCA	GCA	GAA	GAT	GAC	CCT	TCC	CCT	TGT	GCG	CTG	GAA	ACG	960
Ala	Asp	Val	Pro	Ala	Glu	Asp	Asp	Pro	Ser	Pro	Cys	Ala	Leu	Glu	Thr	
305					310					315					320	
GGC	CAC	GGG	CGG	CAG	TGC	CAG	AAC	GGC	ACG	GTG	TGC	AAG	CCC	GGC	TGG	1008
Gly	His	Gly	Arg	Gln	Cys	Gln	Asn	Gly	Thr	Val	Cys	Lys	Pro	Gly	Trp	
				325					330					335		
GAT	GGT	CCC	AAG	CAC	GGC	ATC	ACC	AAC	TTT	GAC	AAC	TTT	GCC	TTC	GCC	1056
Asp	Gly	Pro	Lys	His	Gly	Ile	Thr	Asn	Phe	Asp	Asn	Phe	Ala	Phe	Ala	
			340					345					350			
ATG	CTC	ACG	GTG	TTC	CAG	TGC	ATC	ACC	ATG	GAG	GGC	TGG	ACG	GAC	GTG	1104
Met	Leu	Thr	Val	Phe	Gln	Cys	Ile	Thr	Met	Glu	Gly	Trp	Thr	Asp	Val	
		355					360					365				
CTG	TAC	TGG	GTC	AAT	GAT	GCC	GTA	GGA	AGG	GAC	TGG	CCC	TGG	ATC	TAT	1152

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Leu	Tyr	Trp	Val	Asn	Asp	Ala	Val	Gly	Arg	Asp	Trp	Pro	Trp	Ile	Tyr	
370						375					380					
TTT	GTT	ACA	CTA	ATC	ATC	ATA	GGG	TCA	TTT	TTT	GTA	CTT	AAC	TTG	GTT	1200
Phe	Val	Thr	Leu	Ile	Ile	Ile	Gly	Ser	Phe	Phe	Val	Leu	Asn	Leu	Val	
385					390					395					400	
CTC	GGT	GTG	CTT	AGC	GGA	GAG	TTT	TCC	AAA	GAG	AGG	GAG	AAG	GCC	AAG	1248
Leu	Gly	Val	Leu	Ser	Gly	Glu	Phe	Ser	Lys	Glu	Arg	Glu	Lys	Ala	Lys	
				405					410					415		
GCC	CGG	GGA	GAT	TTC	CAG	AAG	CTG	CGG	GAG	AAG	CAG	CAG	CTA	GAA	GAG	1296
Ala	Arg	Gly	Asp	Phe	Gln	Lys	Leu	Arg	Glu	Lys	Gln	Gln	Leu	Glu	Glu	
			420					425					430			
GAT	CTC	AAA	GGC	TAC	CTG	GAT	TGG	ATC	ACT	CAG	GCC	GAA	GAC	ATC	GAT	1344
Asp	Leu	Lys	Gly	Tyr	Leu	Asp	Trp	Ile	Thr	Gln	Ala	Glu	Asp	Ile	Asp	
		435					440					445				
CCT	GAG	AAT	GAG	GAC	GAA	GGC	ATG	GAT	GAG	GAG	AAG	CCC	CGA	AAC	AGA	1392
Pro	Glu	Asn	Glu	Asp	Glu	Gly	Met	Asp	Glu	Glu	Lys	Pro	Arg	Asn	Arg	
	450					455					460					
GGC	ACT	CCG	GCG	GGC	ATG	CTT	GAT	CAG	AAG	AAA	GGG	AAG	TTT	GCT	TGG	1440
Gly	Thr	Pro	Ala	Gly	Met	Leu	Asp	Gln	Lys	Lys	Gly	Lys	Phe	Ala	Trp	
465					470					475					480	
TTT	AGT	CAC	TCC	ACA	GAA	ACC	CAT	GTG	AGC	ATG	CCC	ACC	AGT	GAG	ACC	1488
Phe	Ser	His	Ser	Thr	Glu	Thr	His	Val	Ser	Met	Pro	Thr	Ser	Glu	Thr	
				485					490					495		
GAG	TCC	GTC	AAC	ACC	GAA	AAC	GTG	GCT	GGA	GGT	GAC	ATC	GAG	GGA	GAA	1536
Glu	Ser	Val	Asn	Thr	Glu	Asn	Val	Ala	Gly	Gly	Asp	Ile	Glu	Gly	Glu	
			500					505					510			
AAC	TGC	GGG	GCC	AGG	CTG	GCC	CAC	CGG	ATC	TCC	AAG	TCA	AAG	TTC	AGC	1584
Asn	Cys	Gly	Ala	Arg	Leu	Ala	His	Arg	Ile	Ser	Lys	Ser	Lys	Phe	Ser	
		515					520					525				
CGC	TAC	TGG	CGC	CGG	TGG	AAT	CGG	TTC	TGC	AGA	AGG	AAG	TGC	CGC	GCC	1632
Arg	Tyr	Trp	Arg	Arg	Trp	Asn	Arg	Phe	Cys	Arg	Arg	Lys	Cys	Arg	Ala	
	530					535					540					
GCA	GTC	AAG	TCT	AAT	GTC	TTC	TAC	TGG	CTG	GTG	ATT	TTC	CTG	GTG	TTC	1680
Ala	Val	Lys	Ser	Asn	Val	Phe	Tyr	Trp	Leu	Val	Ile	Phe	Leu	Val	Phe	
545					550					555					560	
CTC	AAC	ACG	CTC	ACC	ATT	GCC	TCT	GAG	CAC	TAC	AAC	CAG	CCC	AAC	TGG	1728
Leu	Asn	Thr	Leu	Thr	Ile	Ala	Ser	Glu	His	Tyr	Asn	Gln	Pro	Asn	Trp	
				565				570						575		
CTC	ACA	GAA	GTC	CAA	GAC	ACG	GCA	AAC	AAG	GCC	CTG	CTG	GCC	CTG	TTC	1776
Leu	Thr	Glu	Val	Gln	Asp	Thr	Ala	Asn	Lys	Ala	Leu	Leu	Ala	Leu	Phe	
			580					585					590			
ACG	GCA	GAG	ATG	CTC	CTG	AAG	ATG	TAC	AGC	CTG	GGC	CTG	CAG	GCC	TAC	1824

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Thr	Ala	Glu	Met	Leu	Leu	Lys	Met	Tyr	Ser	Leu	Gly	Leu	Gln	Ala	Tyr	
		595					600					605				
TTC	GTG	TCC	CTC	TTC	AAC	CGC	TTT	GAC	TGC	TTC	GTC	GTG	TGT	GGC	GGC	1872
Phe	Val	Ser	Leu	Phe	Asn	Arg	Phe	Asp	Cys	Phe	Val	Val	Cys	Gly	Gly	
	610					615					620					
ATC	CTG	GAG	ACC	ATC	CTG	GTG	GAG	ACC	AAG	ATC	ATG	TCC	CCA	CTG	GGC	1920
Ile	Leu	Glu	Thr	Ile	Leu	Val	Glu	Thr	Lys	Ile	Met	Ser	Pro	Leu	Gly	
	625					630				635					640	
ATC	TCC	GTG	CTC	AGA	TGC	GTC	CGG	CTG	CTG	AGG	ATT	TTC	AAG	ATC	ACG	1968
Ile	Ser	Val	Leu	Arg	Cys	Val	Arg	Leu	Leu	Arg	Ile	Phe	Lys	Ile	Thr	
				645						650					655	
AGG	TAC	TGG	AAC	TCC	TTG	AGC	AAC	CTG	GTG	GCA	TCC	TTG	CTG	AAC	TCT	2016
Arg	Tyr	Trp	Asn	Ser	Leu	Ser	Asn	Leu	Val	Ala	Ser	Leu	Leu	Asn	Ser	
			660					665						670		
GTG	CGC	TCC	ATC	GCC	TCC	CTG	CTC	CTT	CTC	CTC	TTC	CTC	TTC	ATC	ATC	2064
Val	Arg	Ser	Ile	Ala	Ser	Leu	Leu	Leu	Leu	Leu	Phe	Leu	Phe	Ile	Ile	
		675					680									
ATC	TTC	TCC	CTC	CTG	GGG	ATG	CAG	CTC	TTT	GGA	GGA	AAG	TTC	AAC	TTT	2112
Ile	Phe	Ser	Leu	Leu	Gly	Met	Gln	Leu	Phe	Gly	Gly	Lys	Phe	Asn	Phe	
	690					695					700					
GAT	GAG	ATG	CAG	ACC	CGG	AGG	AGC	ACA	TTC	GAT	AAC	TTC	CCC	CAG	TCC	2160
Asp	Glu	Met	Gln	Thr	Arg	Arg	Ser	Thr	Phe	Asp	Asn	Phe	Pro	Gln	Ser	
	705				710					715					720	
CTC	CTC	ACT	GTG	TTT	CAG	ATC	CTG	ACC	GGG	GAG	GAC	TGG	AAT	TCG	GTG	2208
Leu	Leu	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gly	Glu	Asp	Trp	Asn	Ser	Val	
				725					730						735	
ATG	TAT	GAT	GGG	ATC	ATG	GCT	TAT	GGG	GGC	CCC	TCT	TTT	CCA	GGG	ATG	2256
Met	Tyr	Asp	Gly	Ile	Met	Ala	Tyr	Gly	Gly	Pro	Ser	Phe	Pro	Gly	Met	
			740					745						750		
TTA	GTC	TGT	ATT	TAC	TTC	ATC	ATC	CTC	TTC	ATC	TGT	GGA	AAC	TAT	ATC	2304
Leu	Val	Cys	Ile	Tyr	Phe	Ile	Ile	Leu	Phe	Ile	Cys	Gly	Asn	Tyr	Ile	
		755						760								
CTA	CTG	AAT	GTG	TTC	TTG	GCC	ATT	GCT	GTG	GAC	AAC	CTG	GCT	GAT	GCT	2352
Leu	Leu	Asn	Val	Phe	Leu	Ala	Ile	Ala	Val	Asp	Asn	Leu	Ala	Asp	Ala	
	770					775					780					
GAG	AGC	CTC	ACA	TCT	GCC	CAA	AAG	GAG	GAG	GAA	GAG	GAG	AAG	GAG	AGA	2400
Glu	Ser	Leu	Thr	Ser	Ala	Gln	Lys	Glu	Glu	Glu	Glu	Glu	Lys	Glu	Arg	
	785					790				795					800	
AAG	AAG	CTG	GCC	AGG	ACT	GCC	AGC	CCA	GAG	AAG	AAA	CAA	GAG	TTG	GTG	2448
Lys	Lys	Leu	Ala	Arg	Thr	Ala	Ser	Pro	Glu	Lys	Lys	Gln	Glu	Leu	Val	
				805					810						815	
GAG	AAG	CCG	GCA	GTG	GGG	GAA	TCC	AAG	GAG	GAG	AAG	ATT	GAG	CTG	AAA	2496

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Glu	Lys	Pro	Ala	Val	Gly	Glu	Ser	Lys	Glu	Glu	Lys	Ile	Glu	Leu	Lys	
			820					825					830			
TCC	ATC	ACG	GCT	GAC	GGA	GAG	TCT	CCA	CCC	GCC	ACC	AAG	ATC	AAC	ATG	2544
Ser	Ile	Thr	Ala	Asp	Gly	Glu	Ser	Pro	Pro	Ala	Thr	Lys	Ile	Asn	Met	
		835					840					845				
GAT	GAC	CTC	CAG	CCC	AAT	GAA	AAT	GAG	GAT	AAG	AGC	CCC	TAC	CCC	AAC	2592
Asp	Asp	Leu	Gln	Pro	Asn	Glu	Asn	Glu	Asp	Lys	Ser	Pro	Tyr	Pro	Asn	
	850					855					860					
CCA	GAA	ACT	ACA	GGA	GAA	GAG	GAT	GAG	GAG	GAG	CCA	GAG	ATG	CCT	GTC	2640
Pro	Glu	Thr	Thr	Gly	Glu	Glu	Asp	Glu	Glu	Glu	Pro	Glu	Met	Pro	Val	
865					870					875					880	
GGC	CCT	CGC	CCA	CGA	CCA	CTC	TCT	GAG	CTT	CAC	CTT	AAG	GAA	AAG	GCA	2688
Gly	Pro	Arg	Pro	Arg	Pro	Leu	Ser	Glu	Leu	His	Leu	Lys	Glu	Lys	Ala	
				885					890					895		
GTG	CCC	ATG	CCA	GAA	GCC	AGC	GCG	TTT	TTC	ATC	TTC	AGC	TCT	AAC	AAC	2736
Val	Pro	Met	Pro	Glu	Ala	Ser	Ala	Phe	Phe	Ile	Phe	Ser	Ser	Asn	Asn	
			900					905					910			
AGG	TTT	CGC	CTC	CAG	TGC	CAC	CGC	ATT	GTC	AAT	GAC	ACG	ATC	TTC	ACC	2784
Arg	Phe	Arg	Leu	Gln	Cys	His	Arg	Ile	Val	Asn	Asp	Thr	Ile	Phe	Thr	
		915					920					925				
AAC	CTG	ATC	CTC	TTC	TTC	ATT	CTG	CTC	AGC	AGC	ATT	TCC	CTG	GCT	GCT	2832
Asn	Leu	Ile	Leu	Phe	Phe	Ile	Leu	Leu	Ser	Ser	Ile	Ser	Leu	Ala	Ala	
	930					935					940					
GAG	GAC	CCG	GTC	CAG	CAC	ACC	TCC	TTC	AGG	AAC	CAT	ATT	CTG	TTT	TAT	2880
Glu	Asp	Pro	Val	Gln	His	Thr	Ser	Phe	Arg	Asn	His	Ile	Leu	Phe	Tyr	
945					950					955					960	
TTT	GAT	ATT	GTT	TTT	ACC	ACC	ATT	TTC	ACC	ATT	GAA	ATT	GCT	CTG	AAG	2928
Phe	Asp	Ile	Val	Phe	Thr	Thr	Ile	Phe	Thr	Ile	Glu	Ile	Ala	Leu	Lys	
				965					970					975		
ATG	ACT	GCT	TAT	GGG	GCT	TTC	TTG	CAC	AAG	GGT	TCT	TTC	TGC	CGG	AAC	2976
Met	Thr	Ala	Tyr	Gly	Ala	Phe	Leu	His	Lys	Gly	Ser	Phe	Cys	Arg	Asn	
			980					985					990			
TAC	TTC	AAC	ATC	CTG	GAC	CTG	CTG	GTG	GTC	AGC	GTG	TCC	CTC	ATC	TCC	3024
Tyr	Phe	Asn	Ile	Leu	Asp	Leu	Leu	Val	Val	Ser	Val	Ser	Leu	Ile	Ser	
		995					1000					1005				
TTT	GGC	ATC	CAG	TCC	AGT	GCA	ATC	AAT	GTC	GTG	AAG	ATC	TTG	CGA	GTC	3072
Phe	Gly	Ile	Gln	Ser	Ser	Ala	Ile	Asn	Val	Val	Lys	Ile	Leu	Arg	Val	
	1010					1015					1020					
CTG	CGA	GTA	CTC	AGG	CCC	CTG	AGG	GCC	ATC	AAC	AGG	GCC	AAG	GGG	CTA	3120
Leu	Arg	Val	Leu	Arg	Pro	Leu	Arg	Ala	Ile	Asn	Arg	Ala	Lys	Gly	Leu	
1025					1030					1035				1040		
AAG	CAT	GTG	GTT	CAG	TGT	GTG	TTT	GTC	GCC	ATC	CGG	ACC	ATC	GGG	AAC	3168

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Lys	His	Val	Val	Gln	Cys	Val	Phe	Val	Ala	Ile	Arg	Thr	Ile	Gly	Asn	
				1045					1050					1055		
ATC	GTG	ATT	GTC	ACC	ACC	CTG	CTG	CAG	TTC	ATG	TTT	GCC	TGC	ATC	GGG	3216
Ile	Val	Ile	Val	Thr	Thr	Leu	Leu	Gln	Phe	Met	Phe	Ala	Cys	Ile	Gly	
			1060					1065					1070			
GTC	CAG	CTC	TTC	AAG	GGA	AAG	CTG	TAC	ACC	TGT	TCA	GAC	AGT	TCC	AAG	3264
Val	Gln	Leu	Phe	Lys	Gly	Lys	Leu	Tyr	Thr	Cys	Ser	Asp	Ser	Ser	Lys	
		1075					1080					1085				
CAG	ACA	GAG	GCG	GAA	TGC	AAG	GGC	AAC	TAC	ATC	ACG	TAC	AAA	GAC	GGG	3312
Gln	Thr	Glu	Ala	Glu	Cys	Lys	Gly	Asn	Tyr	Ile	Thr	Tyr	Lys	Asp	Gly	
	1090					1095					1100					
GAG	GTT	GAC	CAC	CCC	ATC	ATC	CAA	CCC	CGC	AGC	TGG	GAG	AAC	AGC	AAG	3360
Glu	Val	Asp	His	Pro	Ile	Ile	Gln	Pro	Arg	Ser	Trp	Glu	Asn	Ser	Lys	
1105					1110					1115					1120	
TTT	GAC	TTT	GAC	AAT	GTT	CTG	GCA	GCC	ATG	ATG	GCC	CTC	TTC	ACC	GTC	3408
Phe	Asp	Phe	Asp	Asn	Val	Leu	Ala	Ala	Met	Met	Ala	Leu	Phe	Thr	Val	
				1125					1130					1135		
TCC	ACC	TTC	GAA	GGG	TGG	CCA	GAG	CTG	CTG	TAC	CGC	TCC	ATC	GAC	TCC	3456
Ser	Thr	Phe	Glu	Gly	Trp	Pro	Glu	Leu	Leu	Tyr	Arg	Ser	Ile	Asp	Ser	
			1140					1145					1150			
CAC	ACG	GAA	GAC	AAG	GGC	CCC	ATC	TAC	AAC	TAC	CGT	GTG	GAG	ATC	TCC	3504
His	Thr	Glu	Asp	Lys	Gly	Pro	Ile	Tyr	Asn	Tyr	Arg	Val	Glu	Ile	Ser	
		1155					1160					1165				
ATC	TTC	TTC	ATC	ATC	TAC	ATC	ATC	ATC	ATC	GCC	TTC	TTC	ATG	ATG	AAC	3552
Ile	Phe	Phe	Ile	Ile	Tyr	Ile	Ile	Ile	Ile	Ala	Phe	Phe	Met	Met	Asn	
	1170					1175				1180						
ATC	TTC	GTG	GGC	TTC	GTC	ATC	GTC	ACC	TTT	CAG	GAG	CAG	GGG	GAG	CAG	3600
Ile	Phe	Val	Gly	Phe	Val	Ile	Val	Thr	Phe	Gln	Glu	Gln	Gly	Glu	Gln	
1185					1190					1195					1200	
GAG	TAC	AAG	AAC	TGT	GAG	CTG	GAC	AAG	AAC	CAG	CGA	CAG	TGC	GTG	GAA	3648
Glu	Tyr	Lys	Asn	Cys	Glu	Leu	Asp	Lys	Asn	Gln	Arg	Gln	Cys	Val	Glu	
			1205					1210					1215			
TAC	GCC	CTC	AAG	GCC	CGG	CCC	CTG	CGG	AGG	TAC	ATC	CCC	AAG	AAC	CAG	3696
Tyr	Ala	Leu	Lys	Ala	Arg	Pro	Leu	Arg	Arg	Tyr	Ile	Pro	Lys	Asn	Gln	
			1220					1225					1230			
CAC	CAG	TAC	AAA	GTG	TGG	TAC	GTG	GTC	AAC	TCC	ACC	TAC	TTC	GAG	TAC	3744
His	Gln	Tyr	Lys	Val	Trp	Tyr	Val	Val	Asn	Ser	Thr	Tyr	Phe	Glu	Tyr	
		1235					1240					1245				
CTG	ATG	TTC	GTC	CTC	ATC	CTG	CTC	AAC	ACC	ATC	TGC	CTG	GCC	ATG	CAG	3792
Leu	Met	Phe	Val	Leu	Ile	Leu	Leu	Asn	Thr	Ile	Cys	Leu	Ala	Met	Gln	
	1250					1255					1260					
CAC	TAC	GGC	CAG	AGC	TGC	CTG	TTC	AAA	ATC	GCC	ATG	AAC	ATC	CTC	AAC	3840

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His Tyr Gly Gln Ser Cys Leu Phe Lys Ile Ala Met Asn Ile Leu Asn 1265 1270 1275 1280	
ATG CTC TTC ACT GGC CTC TTC ACC GTG GAG ATG ATC CTG AAG CTC ATT Met Leu Phe Thr Gly Leu Phe Thr Val Glu Met Ile Leu Lys Leu Ile 1285 1290 1295	3888
GCC TTC AAA CCC AAG GGT TAC TTT AGT GAT CCC TGG AAT GTT TTT GAC Ala Phe Lys Pro Lys Gly Tyr Phe Ser Asp Pro Trp Asn Val Phe Asp 1300 1305 1310	3936
TTC CTC ATC GTA ATT GGC AGC ATA ATT GAC GTC ATT CTC AGT GAG ACT Phe Leu Ile Val Ile Gly Ser Ile Ile Asp Val Ile Leu Ser Glu Thr 1315 1320 1325	3984
AAT CCA GCT GAA CAT ACC CAA TGC TCT CCC TCT ATG AAC GCA GAG GAA Asn Pro Ala Glu His Thr Gln Cys Ser Pro Ser Met Asn Ala Glu Glu 1330 1335 1340	4032
AAC TCC CGC ATC TCC ATC ACC TTC TTC CGC CTG TTC CGG GTC ATG CGT Asn Ser Arg Ile Ser Ile Thr Phe Phe Arg Leu Phe Arg Val Met Arg 1345 1350 1355 1360	4080
CTG GTG AAG CTG CTG AGC CGT GGG GAG GGC ATC CGG ACG CTG CTG TGG Leu Val Lys Leu Leu Ser Arg Gly Glu Gly Ile Arg Thr Leu Leu Trp 1365 1370 1375	4128
ACC TTC ATC AAG TCC TTC CAG GCC CTG CCC TAT GTG GCC CTC CTG ATC Thr Phe Ile Lys Ser Phe Gln Ala Leu Pro Tyr Val Ala Leu Leu Ile 1380 1385 1390	4176
GTG ATG CTG TTC TTC ATC TAC GCG GTG ATC GGG ATG CAG GTG TTT GGG Val Met Leu Phe Phe Ile Tyr Ala Val Ile Gly Met Gln Val Phe Gly 1395 1400 1405	4224
AAA ATT GCC CTG AAT GAT ACC ACA GAG ATC AAC CGG AAC AAC AAC TTT Lys Ile Ala Leu Asn Asp Thr Thr Glu Ile Asn Arg Asn Asn Asn Phe 1410 1415 1420	4272
CAG ACC TTC CCC CAG GCC GTG CTG CTC CTC TTC AGG TGT GCC ACC GGG Gln Thr Phe Pro Gln Ala Val Leu Leu Leu Phe Arg Cys Ala Thr Gly 1425 1430 1435 1440	4320
GAG GCC TGG CAG GAC ATC ATG CTG GCC TGC ATG CCA GGC AAG AAG TGT Glu Ala Trp Gln Asp Ile Met Leu Ala Cys Met Pro Gly Lys Lys Cys 1445 1450 1455	4368
GCC CCA GAG TCC GAG CCC AGC AAC AGC ACG GAG GGT GAA ACA CCC TGT Ala Pro Glu Ser Glu Pro Ser Asn Ser Thr Glu Gly Glu Thr Pro Cys 1460 1465 1470	4416
GGT AGC AGC TTT GCT GTC TTC TAC TTC ATC AGC TTC TAC ATG CTC TGT Gly Ser Ser Phe Ala Val Phe Tyr Phe Ile Ser Phe Tyr Met Leu Cys 1475 1480 1485	4464
GCC TTC CTG ATC ATC AAC CTC TTT GTA GCT GTC ATC ATG GAC AAC TTT	4512

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Ala	Phe	Leu	Ile	Ile	Asn	Leu	Phe	Val	Ala	Val	Ile	Met	Asp	Asn	Phe		
1490						1495					1500						
GAC	TAC	CTG	ACA	AGG	GAC	TGG	TCC	ATC	CTT	GGT	CCC	CAC	CAC	CTG	GAT	4560	
Asp	Tyr	Leu	Thr	Arg	Asp	Trp	Ser	Ile	Leu	Gly	Pro	His	His	Leu	Asp		
1505					1510					1515					1520		
GAG	TTT	AAA	AGA	ATC	TGG	GCA	GAG	TAT	GAC	CCT	GAA	GCC	AAG	GGT	CGT	4608	
Glu	Phe	Lys	Arg	Ile	Trp	Ala	Glu	Tyr	Asp	Pro	Glu	Ala	Lys	Gly	Arg		
				1525					1530					1535			
ATC	AAA	CAC	CTG	GAT	GTG	GTG	ACC	CTC	CTC	CGG	CGG	ATT	CAG	CCG	CCA	4656	
Ile	Lys	His	Leu	Asp	Val	Val	Thr	Leu	Leu	Arg	Arg	Ile	Gln	Pro	Pro		
			1540					1545					1550				
CTA	GGT	TTT	GGG	AAG	CTG	TGC	CCT	CAC	CGC	GTG	GCT	TGC	AAA	CGC	CTG	4704	
Leu	Gly	Phe	Gly	Lys	Leu	Cys	Pro	His	Arg	Val	Ala	Cys	Lys	Arg	Leu		
		1555					1560					1565					
GTC	TCC	ATG	AAC	ATG	CCT	CTG	AAC	AGC	GAC	GGG	ACA	GTC	ATG	TTC	AAT	4752	
Val	Ser	Met	Asn	Met	Pro	Leu	Asn	Ser	Asp	Gly	Thr	Val	Met	Phe	Asn		
	1570					1575					1580						
GCC	ACC	CTG	TTT	GCC	CTG	GTC	AGG	ACG	GCC	CTG	AGG	ATC	AAA	ACA	GAA	4800	
Ala	Thr	Leu	Phe	Ala	Leu	Val	Arg	Thr	Ala	Leu	Arg	Ile	Lys	Thr	Glu		
1585					1590					1595					1600		
GGG	AAC	CTA	GAA	CAA	GCC	AAT	GAG	GAG	CTG	CGG	GCG	ATC	ATC	AAG	AAG	4848	
Gly	Asn	Leu	Glu	Gln	Ala	Asn	Glu	Glu	Leu	Arg	Ala	Ile	Ile	Lys	Lys		
				1605					1610					1615			
ATC	TGG	AAG	CGG	ACC	AGC	ATG	AAG	CTG	GAC	CAG	GTG	GTG	CCC	CCT		4896	
Ile	Trp	Lys	Arg	Thr	Ser	Met	Lys	Leu	Leu	Asp	Gln	Val	Val	Pro	Pro		
			1620					1625					1630				
GCA	GGT	GAT	GAT	GAG	GTC	ACC	GTT	GGC	AAG	TTC	TAC	GCC	ACG	TTC	CTG	4944	
Ala	Gly	Asp	Asp	Glu	Val	Thr	Val	Gly	Lys	Phe	Tyr	Ala	Thr	Phe	Leu		
		1635					1640					1645					
ATC	CAG	GAG	TAC	TTC	CGG	AAG	TTC	AAG	AAG	CGC	AAA	GAG	CAG	GGC	CTT	4992	
Ile	Gln	Glu	Tyr	Phe	Arg	Lys	Phe	Lys	Lys	Arg	Lys	Glu	Gln	Gly	Leu		
	1650					1655					1660						
GTG	GGC	AAG	CCC	TCC	CAG	AGG	AAC	GCG	CTG	TCT	CTG	CAG	GCT	GGC	TTG	5040	
Val	Gly	Lys	Pro	Ser	Gln	Arg	Asn	Ala	Leu	Ser	Leu	Gln	Ala	Gly	Leu		
1665					1670					1675					1680		
CGC	ACA	CTG	CAT	GAC	ATC	GGG	CCT	GAG	ATC	CGA	CGG	GCC	ATC	TCT	GGA	5088	
Arg	Thr	Leu	His	Asp	Ile	Gly	Pro	Glu	Ile	Arg	Arg	Ala	Ile	Ser	Gly		
				1685					1690					1695			
GAT	CTC	ACC	GCT	GAG	GAG	GAG	CTG	GAC	AAG	GCC	ATG	AAG	GAG	GCT	GTG	5136	
Asp	Leu	Thr	Ala	Glu	Glu	Glu	Leu	Asp	Lys	Ala	Met	Lys	Glu	Ala	Val		
			1700					1705					1710				
TCC	GCT	GCT	TCT	GAA	GAT	GAC	ATC	TTC	AGG	AGG	GCC	GGT	GGC	CTG	TTC	5184	

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Ser	Ala	Ala	Ser	Glu	Asp	Asp	Ile	Phe	Arg	Arg	Ala	Gly	Gly	Leu	Phe		
	1715						1720					1725					
GGC	AAC	CAC	GTC	AGC	TAC	TAC	CAA	AGC	GAC	GGC	CGG	AGC	GCC	TTC	CCC	5232	
Gly	Asn	His	Val	Ser	Tyr	Tyr	Gln	Ser	Asp	Gly	Arg	Ser	Ala	Phe	Pro		
	1730					1735				1740							
CAG	ACC	TTC	ACC	ACT	CAG	CGC	CCG	CTG	CAC	ATC	AAC	AAG	GCG	GGC	AGC	5280	
Gln	Thr	Phe	Thr	Thr	Gln	Arg	Pro	Leu	His	Ile	Asn	Lys	Ala	Gly	Ser		
	1745				1750				1755						1760		
AGC	CAG	GGC	GAC	ACT	GAG	TCG	CCA	TCC	CAC	GAG	AAG	CTG	GTG	GAC	TCC	5328	
Ser	Gln	Gly	Asp	Thr	Glu	Ser	Pro	Ser	His	Glu	Lys	Leu	Val	Asp	Ser		
				1765					1770					1775			
ACC	TTC	ACC	CCG	AGC	AGC	TAC	TCG	TCC	ACC	GGC	TCC	AAC	GCC	AAC	ATC	5376	
Thr	Phe	Thr	Pro	Ser	Ser	Tyr	Ser	Ser	Thr	Gly	Ser	Asn	Ala	Asn	Ile		
			1780				1785					1790					
AAC	AAC	GCC	AAC	AAC	ACC	GCC	CTG	GGT	CGC	CTC	CCT	CGC	CCC	GCC	GGC	5424	
Asn	Asn	Ala	Asn	Asn	Thr	Ala	Leu	Gly	Arg	Leu	Pro	Arg	Pro	Ala	Gly		
		1795					1800					1805					
TAC	CCC	AGC	ACA	GTC	AGC	ACT	GTG	GAG	GGC	CAC	GGG	CCC	CCC	TTG	TCC	5472	
Tyr	Pro	Ser	Thr	Val	Ser	Thr	Val	Glu	Gly	His		Pro	Pro	Leu	Ser		
	1810					1815				1820							
CCT	GCC	ATC	CGG	GTG	CAG	GAG	GTG	GCG	TGG	AAG	CTC	AGC	TCC	AAC	AGG	5520	
Pro	Ala	Ile	Arg	Val	Gln	Glu	Val	Ala	Trp	Lys	Leu	Ser	Ser	Asn	Arg		
	1825				1830				1835						1840		
TGC	CAC	TCC	CGG	GAG	AGC	CAG	GCA	GCC	ATG	GCG	CGT	CAG	GAG	GAG	ACG	5568	
Cys	His	Ser	Arg	Glu	Ser	Gln	Ala	Ala	Met	Ala	Arg	Gln	Glu	Glu	Thr		
				1845					1850					1855			
TCT	CAG	GAT	GAG	ACC	TAT	GAA	GTG	AAG	ATG	AAC	CAT	GAC	ACG	GAG	GCC	5616	
Ser	Gln	Asp	Glu	Thr	Tyr	Glu	Val	Lys	Met	Asn	His	Asp	Thr	Glu	Ala		
			1860				1865						1870				
TGC	AGT	GAG	CCC	AGC	CTG	CTC	TCC	ACA	GAG	ATG	CTC	TCC	TAC	CAG	GAT	5664	
Cys	Ser	Glu	Pro	Ser	Leu	Leu	Ser	Thr	Glu	Met	Leu	Ser	Tyr	Gln	Asp		
		1875					1880					1885					
GAC	GAA	AAT	CGG	CAA	CTG	ACG	CTC	CCA	GAG	GAG	GAC	AAG	AGG	GAC	ATC	5712	
Asp	Glu	Asn	Arg	Gln	Leu	Thr	Leu	Pro	Glu	Glu	Asp	Lys	Arg	Asp	Ile		
	1890					1895					1900						
CGG	CAA	TCT	CCG	AAG	AGG	GGT	TTC	CTC	CGC	TCT	GCC	TCA	CTA	GGT	CGA	5760	
Arg	Gln	Ser	Pro	Lys	Arg	Gly	Phe	Leu	Arg	Ser	Ala	Ser	Leu	Gly	Arg		
	1905				1910					1915					1920		
AGG	GCC	TCC	TTC	CAC	CTG	GAA	TGT	CTG	AAG	CGA	CAG	AAG	GAC	CGA	GGG	5808	
Arg	Ala	Ser	Phe	His	Leu	Glu	Cys	Leu	Lys	Arg	Gln	Lys	Asp	Arg	Gly		
				1925					1930					1935			
GGA	GAC	ATC	TCT	CAG	AAG	ACA	GTC	CTG	CCC	TTG	CAT	CTG	GTT	CAT	CAT	5856	

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Gly	Asp	Ile	Ser	Gln	Lys	Thr	Val	Leu	Pro	Leu	His	Leu	Val	His	His	
			1940					1945					1950			
CAG	GCA	TTG	GCA	GTG	GCA	GGC	CTG	AGC	CCC	CTC	CTC	CAG	AGA	AGC	CAT	5904
Gln	Ala	Leu	Ala	Val	Ala	Gly	Leu	Ser	Pro	Leu	Leu	Gln	Arg	Ser	His	
		1955					1960					1965				
TCC	CCT	GCC	TCA	TTC	CCT	AGG	CCT	TTT	GCC	ACC	CCA	CCA	GCC	ACA	CCT	5952
Ser	Pro	Ala	Ser	Phe	Pro	Arg	Pro	Phe	Ala	Thr	Pro	Pro	Ala	Thr	Pro	
	1970					1975					1980					
GGC	AGC	CGA	GGC	TGG	CCC	CCA	CAG	CCC	GTC	CCC	ACC	CTG	CGG	CTT	GAG	6000
Gly	Ser	Arg	Gly	Trp	Pro	Pro	Gln	Pro	Val	Pro	Thr	Leu	Arg	Leu	Glu	
1985					1990					1995					2000	
GGG	GTC	GAG	TCC	AGT	GAG	AAA	CTC	AAC	AGC	AGC	TTC	CCA	TCC	ATC	CAC	6048
Gly	Val	Glu	Ser	Ser	Glu	Lys	Leu	Asn	Ser	Ser	Phe	Pro	Ser	Ile	His	
				2005					2010					2015		
TGC	GGC	TCC	TGG	GCT	GAG	ACC	ACC	CCC	GGT	GGC	GGG	GGC	AGC	AGC	GCC	6096
Cys	Gly	Ser	Trp	Ala	Glu	Thr	Thr	Pro	Gly	Gly	Gly	Gly	Ser	Ser	Ala	
			2020					2025					2030			
GCC	CGG	AGA	GTC	CGG	CCC	GTC	TCC	CTC	ATG	GTG	CCC	AGC	CAG	GCT	GGG	6144
Ala	Arg	Arg	Val	Arg	Pro	Val	Ser	Leu	Met	Val	Pro	Ser	Gln	Ala	Gly	
		2035					2040					2045				
GCC	CCA	GGG	AGG	CAG	TTC	CAC	GGC	AGT	GCC	AGC	AGC	CTG	GTG	GAA	GCG	6192
Ala	Pro	Gly	Arg	Gln	Phe	His	Gly	Ser	Ala	Ser	Ser	Leu	Val	Glu	Ala	
	2050					2055					2060					
GTC	TTG	ATT	TCA	GAA	GGA	CTG	GGG	CAG	TTT	GCT	CAA	GAT	CCC	AAG	TTC	6240
Val	Leu	Ile	Ser	Glu	Gly	Leu	Gly	Gln	Phe	Ala	Gln	Asp	Pro	Lys	Phe	
2070					2075					2080					2085	
ATC	GAG	GTC	ACC	ACC	CAG	GAG	CTG	GCC	GAC	GCC	TGC	GAC	ATG	ACC	ATA	6288
Ile	Glu	Val	Thr	Thr	Gln	Glu	Leu	Ala	Asp	Ala	Cys	Asp	Met	Thr	Ile	
				2090				2095					2100			
GAG	GAG	ATG	GAG	AGC	GCG	GCC	GAC	AAC	ATC	CTC	AGC	GGG	GGC	GCC	CCA	6336
Glu	Glu	Met	Glu	Ser	Ala	Ala	Asp	Asn	Ile	Leu	Ser	Gly	Gly	Ala	Pro	
			2105					2110					2115			
CAG	AGC	CCC	AAT	GGC	GCC	CTC	TTA	CCC	TTT	GTG	AAC	TGC	AGG	GAC	GCG	6384
Gln	Ser	Pro	Asn	Gly	Ala	Leu	Leu	Pro	Phe	Val	Asn	Cys	Arg	Asp	Ala	
		2120					2125					2130				
GGG	CAG	GAC	CGA	GCC	GGG	GGC	GAA	GAG	GAC	GCG	GGC	TGT	GTG	CGC	GCG	6432
Gly	Gln	Asp	Arg	Ala	Gly	Gly	Glu	Glu	Asp	Ala	Gly	Cys	Val	Arg	Ala	
	2135					2135					2140					
CGG	GGT	CGA	CCG	AGT	GAG	GAG	GAG	CTC	CAG	GAC	AGC	AGG	GTC	TAC	GTC	6480
Arg	Gly	Arg	Pro	Ser	Glu	Glu	Glu	Leu	Gln	Asp	Ser	Arg	Val	Tyr	Val	
2145					2150					2155					2160	
AGC	AGC	CTG	TAGTGGGCGC	TGCCAGATGC	GGGCTTTTTT	TTATTTGTTT	CAATGTTCTT									6539

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Ser Ser Leu

AATGGGTTTCG TTTCAGAAGT GCCTCACTGT TCTCGT

6575

(2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 133 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

AGACCACGGC TTCCTCGAAT CTTGCGCGAA GCCGCCGGCCA TCGGAGGAG GGATTAATCC 60
AGACCCGCCG GGGGGTGTTT TCACATTCTC TCCTCTTCGTG GCTGCTCCT CCTATTAAAA 120
CCATTTTGG TCC 133

(2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 89 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CGCTGAGGGC CTTCCGCGTG CTGCGCCCCC TCGGGCTGGT GTCCGGAGTC CCAAGTCTCC 60
AGGTGGTCCT GAATCCATC ATCAAGGCC 89

(2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 84 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..84
- (D) OTHER INFORMATION: /note= "An alternative exon of alpha-1C."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

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CAC	TAT	TTC	TGT	GAT	GCA	TGG	AAT	ACA	TTT	GAC	GCC	TTG	ATT	GTT	GTG	48
His	Tyr	Phe	Cys	Asp	Ala	Trp	Asn	Thr	Phe	Asp	Ala	Leu	Ile	Val	Val	
1				5					10					15		

GGT	AGC	ATT	GTT	GAT	ATA	GCA	ATC	ACC	GAG	GTA	AAC					84
Gly	Ser	Ile	Val	Asp	Ile	Ala	Ile	Thr	Glu	Val	Asn					
			20					25								

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 7362 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 144..7163

(ix) FEATURE:

- (A) NAME/KEY: 5'UTR
- (B) LOCATION: 1..143

(ix) FEATURE:

- (A) NAME/KEY: 3'UTR
- (B) LOCATION: 7161..7362

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GCGGCGGCGG	CTGCGGCGGT	GGGGCCGGGC	GAGGTCCGTG	CGGTCCCGGC	GGCTCCGTGG	60
CTGCTCCGCT	CTGAGCGCCT	GCGCGCCCCG	CGCCCTCCCT	GCCGGGGCCG	CTGGGCGGGG	120
GATGCACGCG	GGGCCCCGGA	GCC ATG	GTC CGC	TTC GGG	GAC GAG	170
		Met Val	Arg Phe	Gly Asp	Glu Leu	
		1		5		
GGC CGC	TAT GGA	GGC CCC	GGC GGC	GGA GAG	CGG GCC	218
Gly Arg	Tyr Gly	Gly Gly	Pro Gly	Gly Gly	Glu Arg	
10		15		20	25	
GCC GGC	GGG GCG	GGG GGC	CCG GGT	CCC GGG	GGG CTG	266
Ala Gly	Gly Ala	Gly Gly	Pro Gly	Pro Gly	Gly Leu	
		30		35	40	
CGG GTC	CTC TAC	AAG CAA	TCG ATC	GCG CAG	CGC GCG	314
Arg Val	Leu Tyr	Lys Gln	Ser Ile	Ala Gln	Arg Ala	
		45		50	55	
CTG TAC	AAC CCC	ATC CCG	GTC AAG	CAG AAC	TGC TTC	362
Leu Tyr	Asn Pro	Ile Pro	Val Lys	Gln Asn	Cys Phe	
		60		65	70	

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TCG	CTC	TTC	GTC	TTC	AGC	GAG	GAC	AAC	GTC	GTC	CGC	AAA	TAC	GCG	AAG	410
Ser	Leu	Phe	Val	Phe	Ser	Glu	Asp	Asn	Val	Val	Arg	Lys	Tyr	Ala	Lys	
	75					80					85					
CGC	ATC	ACC	GAG	TGG	CCT	CCA	TTC	GAG	AAT	ATG	ATC	CTG	GCC	ACC	ATC	458
Arg	Ile	Thr	Glu	Trp	Pro	Pro	Phe	Glu	Asn	Met	Ile	Leu	Ala	Thr	Ile	
90					95					100					105	
ATC	GCC	AAC	TGC	ATC	GTG	CTG	GCC	CTG	GAG	CAG	CAC	CTC	CCT	GAT	GGG	506
Ile	Ala	Asn	Cys	Ile	Val	Leu	Ala	Leu	Glu	Gln	His	Leu	Pro	Asp	Gly	
				110					115					120		
GAC	AAA	ACG	CCC	ATG	TCC	GAG	CGG	CTG	GAC	GAC	ACG	GAG	CCC	TAT	TTC	554
Asp	Lys	Thr	Pro	Met	Ser	Glu	Arg	Leu	Asp	Asp	Thr	Glu	Pro	Tyr	Phe	
			125					130					135			
ATC	GGG	ATC	TTT	TGC	TTC	GAG	GCA	GGG	ATC	AAA	ATC	ATC	GCT	CTG	GGC	602
Ile	Gly	Ile	Phe	Cys	Phe	Glu	Ala	Gly	Ile	Lys	Ile	Ile	Ala	Leu	Gly	
	140						145					150				
TTT	GTC	TTC	CAC	AAG	GGC	TCT	TAC	CTG	CGG	AAC	GGC	TGG	AAC	GTC	ATG	650
Phe	Val	Phe	His	Lys	Gly	Ser	Tyr	Leu	Arg	Asn	Gly	Trp	Asn	Val	Met	
	155					160					165					
GAC	TTC	GTG	GTC	GTC	CTC	ACA	GGG	ATC	CTT	GCC	ACG	GCT	GGA	ACT	GAC	698
Asp	Phe	Val	Val	Val	Leu	Thr	Gly	Ile	Leu	Ala	Thr	Ala	Gly	Thr	Asp	
170					175					180					185	
TTC	GAC	CTG	CGA	ACA	CTG	AGG	GCT	GTG	CGT	GTG	CTG	AGG	CCC	CTG	AAG	746
Phe	Asp	Leu	Arg	Thr	Leu	Arg	Ala	Val	Arg	Val	Leu	Arg	Pro	Leu	Lys	
				190					195					200		
CTG	GTG	TCT	GGG	ATT	CCA	AGT	TTG	CAG	GTG	GTG	CTC	AAG	TCC	ATC	ATG	794
Leu	Val	Ser	Gly	Ile	Pro	Ser	Leu	Gln	Val	Val	Leu	Lys	Ser	Ile	Met	
			205					210					215			
AAG	GCC	ATG	GTT	CCA	CTC	CTG	CAG	ATT	GGG	CTG	CTT	CTC	TTC	TTT	GCC	842
Lys	Ala	Met	Val	Pro	Leu	Leu	Gln	Ile	Gly	Leu	Leu	Leu	Phe	Phe	Ala	
	220						225					230				
ATC	CTC	ATG	TTT	GCC	ATC	ATT	GGC	CTG	GAG	TTC	TAC	ATG	GGC	AAG	TTC	890
Ile	Leu	Met	Phe	Ala	Ile	Ile	Gly	Leu	Glu	Phe	Tyr	Met	Gly	Lys	Phe	
	235					240					245					
CAC	AAG	GCC	TGT	TTC	CCC	AAC	AGC	ACA	GAT	GCG	GAG	CCC	GTG	GGT	GAC	938
His	Lys	Ala	Cys	Phe	Pro	Asn	Ser	Thr	Asp	Ala	Glu	Pro	Val	Gly	Asp	
	250				255					260					265	
TTC	CCC	TGT	GGC	AAG	GAG	GCC	CCA	GCC	CGG	CTG	TGC	GAG	GGC	GAC	ACT	986
Phe	Pro	Cys	Gly	Lys	Glu	Ala	Pro	Ala	Arg	Leu	Cys	Glu	Gly	Asp	Thr	
				270					275					280		
GAG	TGC	CGG	GAG	TAC	TGG	CCA	GGA	CCC	AAC	TTT	GGC	ATC	ACC	AAC	TTT	1034
Glu	Cys	Arg	Glu	Tyr	Trp	Pro	Gly	Pro	Asn	Phe	Gly	Ile	Thr	Asn	Phe	
			285					290					295			

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GAC Asp	AAT Asn	ATC Ile	CTG Leu	TTT Phe	GCC Ala	ATC Ile	TTG Leu	ACG Thr	GTG Val	TTC Phe	CAG Gln	TGC Cys	ATC Ile	ACC Thr	ATG Met	1082
		300					305					310				
GAG Glu	GGC Gly	TGG Trp	ACT Thr	GAC Asp	ATC Ile	CTC Leu	TAT Tyr	AAT Asn	ACA Thr	AAC Asn	GAT Asp	GCG Ala	GCC Ala	GGC Gly	AAC Asn	1130
	315					320					325					
ACC Thr	TGG Trp	AAC Asn	TGG Trp	CTC Leu	TAC Tyr	TTC Phe	ATC Ile	CCT Pro	CTC Leu	ATC Ile	ATC Ile	ATC Ile	GGC Gly	TCC Ser	TTC Phe	1178
330					335					340					345	
TTC Phe	ATG Met	CTC Leu	AAC Asn	CTG Leu	GTG Val	CTG Leu	GGC Gly	GTG Val	CTC Leu	TCG Ser	GGG Gly	GAG Glu	TTT Phe	GCC Ala	AAG Lys	1226
				350					355						360	
GAG Glu	CGA Arg	GAG Glu	AGG Arg	GTG Val	GAG Glu	AAC Asn	CGC Arg	CGC Arg	GCC Ala	TTC Phe	CTG Leu	AAG Lys	CTG Leu	CGC Arg	CGG Arg	1274
			365					370					375			
CAG Gln	CAG Gln	CAG Gln	ATC Ile	GAG Glu	CGA Arg	GAG Glu	CTC Leu	AAC Asn	GGG Gly	TAC Tyr	CTG Leu	GAG Glu	TGG Trp	ATC Ile	TTC Phe	1322
		380					385					390				
AAG Lys	GCG Ala	GAG Glu	GAA Glu	GTC Val	ATG Met	CTG Leu	GCC Ala	GAG Glu	GAG Glu	GAC Asp	AGG Arg	AAT Asn	GCA Ala	GAG Glu	GAG Glu	1370
	395					400					405					
AAG Lys	TCC Ser	CCT Pro	TTG Leu	GAC Asp	GTG Val	CTG Leu	AAG Lys	AGA Arg	GCG Ala	GCC Ala	ACC Thr	AAG Lys	AAG Lys	AGC Ser	AGA Arg	1418
410					415					420					425	
AAT Asn	GAC Asp	CTG Leu	ATC Ile	CAC His	GCA Ala	GAG Glu	GAG Glu	GGA Gly	GAG Glu	GAC Asp	CGG Arg	TTT Phe	GCA Ala	GAT Asp	CTC Leu	1466
				430				435						440		
TGT Cys	GCT Ala	GTT Val	GGA Gly	TCC Ser	CCC Pro	TTC Phe	GCC Ala	CGC Arg	GCC Ala	AGC Ser	CTC Leu	AAG Lys	AGC Ser	GGG Gly	AAG Lys	1514
			445					450					455			
ACA Thr	GAG Glu	AGC Ser	TCG Ser	TCA Ser	TAC Tyr	TTC Phe	CGG Arg	AGG Arg	AAG Lys	GAG Glu	AAG Lys	ATG Met	TTC Phe	CGG Arg	TTT Phe	1562
		460					465					470				
TTT Phe	ATC Ile	CGG Arg	CGC Arg	ATG Met	GTG Val	AAG Lys	GCT Ala	CAG Gln	AGC Ser	TTC Phe	TAC Tyr	TGG Trp	GTG Val	GTG Val	CTG Leu	1610
	475					480					485					
TGC Cys	GTG Val	GTG Val	GCC Ala	CTG Leu	AAC Asn	ACA Thr	CTG Leu	TGT Cys	GTG Val	GCC Ala	ATG Met	GTG Val	CAT His	TAC Tyr	AAC Asn	1658
490					495					500					505	
CAG Gln	CCG Pro	CGG Arg	CGG Arg	CTT Leu	ACC Thr	ACG Thr	ACC Thr	CTG Leu	TAT Tyr	TTT Phe	GCA Ala	GAG Glu	TTT Phe	GTT Val	TTC Phe	1706
				510					515					520		

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CTG	GGT	CTC	TTC	CTC	ACA	GAG	ATG	TCC	CTG	AAG	ATG	TAT	GGC	CTG	GGG	1754
Leu	Gly	Leu	Phe	Leu	Thr	Glu	Met	Ser	Leu	Lys	Met	Tyr	Gly	Leu	Gly	
			525					530					535			
CCC	AGA	AGC	TAC	TTC	CGG	TCC	TCC	TTC	AAC	TGC	TTC	GAC	TTT	GGG	GTC	1802
Pro	Arg	Ser	Tyr	Phe	Arg	Ser	Ser	Phe	Asn	Cys	Phe	Asp	Phe	Gly	Val	
		540					545					550				
ATC	GTG	GGG	AGC	GTC	TTT	GAA	GTG	GTC	TGG	GCG	GCC	ATC	AAG	CCG	GGA	1850
Ile	Val	Gly	Ser	Val	Phe	Glu	Val	Val	Trp	Ala	Ala	Ile	Lys	Pro	Gly	
	555					560					565					
AGC	TCC	TTT	GGG	ATC	AGT	GTG	CTG	CGG	GCC	CTC	CGC	CTG	CTG	AGG	ATC	1898
Ser	Ser	Phe	Gly	Ile	Ser	Val	Leu	Arg	Ala	Leu	Arg	Leu	Leu	Arg	Ile	
570					575					580					585	
TTC	AAA	GTC	ACG	AAG	TAC	TGG	AGC	TCC	CTG	CGG	AAC	CTG	GTG	GTG	TCC	1946
Phe	Lys	Val	Thr	Lys	Tyr	Trp	Ser	Ser	Leu	Arg	Asn	Leu	Val	Val	Ser	
				590					595					600		
CTG	CTG	AAC	TCC	ATG	AAG	TCC	ATC	ATC	AGC	CTG	CTC	TTC	TTG	CTC	TTC	1994
Leu	Leu	Asn	Met	Lys	Ser	Ile	Ile	Ser	Leu	Leu	Phe	Leu	Leu	Phe		
		605				610						615				
CTG	TTC	ATT	GTG	GTC	TTC	GCC	CTG	CTG	GGG	ATG	CAG	CTG	TTT	GGG	GGA	2042
Leu	Phe	Ile	Val	Val	Phe	Ala	Leu	Leu	Gly	Met	Gln	Leu	Phe	Gly	Gly	
		620				625						630				
CAG	TTC	AAC	TTC	CAG	GAT	GAG	ACT	CCC	ACA	ACC	AAC	TTC	GAC	ACC	TTC	2090
Gln	Phe	Asn	Phe	Gln	Asp	Glu	Thr	Pro	Thr	Thr	Asn	Phe	Asp	Thr	Phe	
	635				640						645					
CCT	GCC	GCC	ATC	CTC	ACT	GTC	TTC	CAG	ATC	CTG	ACG	GGA	GAG	GAC	TGG	2138
Pro	Ala	Ala	Ile	Leu	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gly	Glu	Asp	Trp	
650					655					660					665	
AAT	GCA	GTG	ATG	TAT	CAC	GGG	ATC	GAA	TCG	CAA	GGC	GGC	GTC	AGC	AAA	2186
Asn	Ala	Val	Met	Tyr	His	Gly	Ile	Glu	Ser	Gln	Gly	Gly	Val	Ser	Lys	
				670				675						680		
GGC	ATG	TTC	TCG	TCC	TTT	TAC	TTC	ATT	GTC	CTG	ACA	CTG	TTC	GGA	AAC	2234
Gly	Met	Phe	Ser	Ser	Phe	Tyr	Phe	Ile	Val	Leu	Thr	Leu	Phe	Gly	Asn	
			685					690					695			
TAC	ACT	CTG	CTG	AAT	GTC	TTT	CTG	GCC	ATC	GCT	GTG	GAC	AAC	CTG	GCC	2282
Tyr	Thr	Leu	Leu	Asn	Val	Phe	Leu	Ala	Ile	Ala	Val	Asp	Asn	Leu	Ala	
		700				705						710				
AAC	GCC	CAA	GAG	CTG	ACC	AAG	GAT	GAA	GAG	GAG	ATG	GAA	GAA	GCA	GCC	2330
Asn	Ala	Gln	Glu	Leu	Thr	Lys	Asp	Glu	Glu	Glu	Met	Glu	Glu	Ala	Ala	
	715					720					725					
AAT	CAG	AAG	CTT	GCT	CTG	CAA	AAG	GCC	AAA	GAA	GTG	GCT	GAA	GTC	AGC	2378
Asn	Gln	Lys	Leu	Ala	Leu	Gln	Lys	Ala	Lys	Glu	Val	Ala	Glu	Val	Ser	
730					735					740					745	

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CCC	ATG	TCT	GCC	GCG	AAC	ATC	TCC	ATC	GCC	GCC	AGG	CAG	CAG	AAC	TCG	2426
Pro	Met	Ser	Ala	Ala	Asn	Ile	Ser	Ile	Ala	Ala	Arg	Gln	Gln	Asn	Ser	
				750					755					760		
GCC	AAG	GCG	CGC	TCG	GTG	TGG	GAG	CAG	CGG	GCC	AGC	CAG	CTA	CGG	CTG	2474
Ala	Lys	Ala	Arg	Ser	Val	Trp	Glu	Gln	Arg	Ala	Ser	Gln	Leu	Arg	Leu	
			765				770					775				
CAG	AAC	CTG	CGG	GCC	AGC	TGC	GAG	GCG	CTG	TAC	AGC	GAG	ATG	GAC	CCC	2522
Gln	Asn	Leu	Arg	Ala	Ser	Cys	Glu	Ala	Leu	Tyr	Ser	Glu	Met	Asp	Pro	
		780				785						790				
GAG	GAG	CGG	CTG	GCG	TTC	GCC	ACT	ACG	GCG	CAC	CTG	CGG	CCC	GAC	ATG	2570
Glu	Glu	Arg	Leu	Arg	Phe	Ala	Thr	Thr	Arg	His	Leu	Arg	Pro	Asp	Met	
	795				800						805					
AAG	ACG	CAC	CTG	GAC	CGG	CCG	CTG	GTG	GTG	GAG	CTG	GGC	CGC	GAC	GGC	2618
Lys	Thr	His	Leu	Asp	Arg	Pro	Leu	Val	Val	Glu	Leu	Gly	Arg	Asp	Gly	
810				815						820					825	
GCG	CGG	GGG	CCC	GTG	GGA	GGC	AAA	GCC	CGA	CCT	GAG	GCT	GCG	GAG	GCC	2666
Ala	Arg	Gly	Pro	Val	Gly	Gly	Lys	Ala	Arg	Pro	Glu	Ala	Ala	Glu	Ala	
			830					835						840		
CCC	GAG	GGC	GTC	GAC	CCT	CCG	GCG	AGG	CAC	CAC	CGG	CAC	CGC	GAC	AAG	2714
Pro	Glu	Gly	Val	Asp	Pro	Pro	Arg	Arg	His	His	Arg	His	Arg	Asp	Lys	
			845					850					855			
GAC	AAG	ACC	CCC	GCG	GCG	GGG	GAC	CAG	GAC	CGA	GCA	GAG	GCC	CCG	AAG	2762
Asp	Lys	Thr	Pro	Ala	Ala	Gly	Asp	Gln	Asp	Arg	Ala	Glu	Ala	Pro	Lys	
		860				865						870				
GCG	GAG	AGC	GGG	GAG	CCC	GGT	GCC	CGG	GAG	GAG	CGG	CCG	CGG	CCG	CAC	2810
Ala	Glu	Ser	Gly	Glu	Pro	Gly	Ala	Arg	Glu	Glu	Arg	Pro	Arg	Pro	His	
	875				880						885					
CGC	AGC	CAC	AGC	AAG	GAG	GCC	GCG	GGG	CCC	CCG	GAG	GCG	CGG	AGC	GAG	2858
Arg	Ser	His	Ser	Lys	Glu	Ala	Ala	Gly	Pro	Pro	Glu	Ala	Arg	Ser	Glu	
890				895					900						905	
CGC	GGC	CGA	GGC	CCA	GGC	CCC	GAG	GGC	GGC	CGG	CGG	CAC	CAC	CGG	CGC	2906
Arg	Gly	Arg	Gly	Pro	Gly	Pro	Glu	Gly	Gly	Arg	Arg	His	His	Arg	Arg	
			910					915						920		
GGC	TCC	CCG	GAG	GAG	GCG	GCC	GAG	CGG	GAG	CCC	CGA	CGC	CAC	CGC	GCG	2954
Gly	Ser	Pro	Glu	Glu	Ala	Ala	Glu	Arg	Glu	Pro	Arg	Arg	His	Arg	Ala	
			925				930						935			
CAC	CGG	CAC	CAG	GAT	CCG	AGC	AAG	GAG	TGC	GCC	GGC	GCC	AAG	GGC	GAG	3002
His	Arg	His	Gln	Asp	Pro	Ser	Lys	Glu	Cys	Ala	Gly	Ala	Lys	Gly	Glu	
		940					945					950				
CGG	CGC	GCG	CGG	CAC	CGC	GGC	GGC	CCC	CGA	GCG	GGG	CCC	CGG	GAG	GCG	3050
Arg	Arg	Ala	Arg	His	Arg	Gly	Gly	Pro	Arg	Ala	Gly	Pro	Arg	Glu	Ala	
	955					960					965					

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GAG AGC GGG GAG GAG CCG GCG CGG CGG CAC CGG GCC CGG CAC AAG GCG Glu Ser Gly Glu Glu Pro Ala Arg Arg His Arg Ala Arg His Lys Ala 970 975 980 985	3098
CAG CCT GCT CAC GAG GCT GTG GAG AAG GAG ACC ACG GAG AAG GAG GCC Gln Pro Ala His Glu Ala Val Glu Lys Glu Thr Thr Glu Lys Glu Ala 990 995 1000	3146
ACG GAG AAG GAG GCT GAG ATA GTG GAA GCC GAC AAG GAA AAG GAG CTC Thr Glu Lys Glu Ala Glu Ile Val Glu Ala Asp Lys Glu Lys Glu Leu 1005 1010 1015	3194
CGG AAC CAC CAG CCC CGG GAG CCA CAC TGT GAC CTG GAG ACC AGT GGG Arg Asn His Gln Pro Arg Glu Pro His Cys Asp Leu Glu Thr Ser Gly 1020 1025 1030	3242
ACT GTG ACT GTG GGT CCC ATG CAC ACA CTG CCC AGC ACC TGT CTC CAG Thr Val Thr Val Gly Pro Met His Thr Leu Pro Ser Thr Cys Leu Gln 1035 1040 1045	3290
AAG GTG GAG GAA CAG CCA GAG GAT GCA GAC AAT CAG CGG AAC GTC ACT Lys Val Glu Glu Gln Pro Glu Asp Ala Asp Asn Gln Arg Asn Val Thr 1050 1055 1060 1065	3338
CGC ATG GGC AGT CAG CCC CCA GAC CCG AAC ACT ATT GTA CAT ATC CCA Arg Met Gly Ser Gln Pro Pro Asp Pro Asn Thr Ile Val His Ile Pro 1070 1075 1080	3386
GTG ATG CTG ACG GGC CCT CTT GGG GAA GCC ACG GTC GTT CCC AGT GGT Val Met Leu Thr Gly Pro Leu Gly Glu Ala Thr Val Val Pro Ser Gly 1085 1090 1095	3434
AAC GTG GAC CTG GAA AGC CAA GCA GAG GGG AAG AAG GAG GTG GAA GCG Asn Val Asp Leu Glu Ser Gln Ala Glu Gly Lys Lys Glu Val Glu Ala 1100 1105 1110	3482
GAT GAC GTG ATG AGG AGC GGC CCC CGG CCT ATC GTC CCA TAC AGC TCC Asp Asp Val Met Arg Ser Gly Pro Arg Pro Ile Val Pro Tyr Ser Ser 1115 1120 1125	3530
ATG TTC TGT TTA AGC CCC ACC AAC CTG CTC CGC CGC TTC TGC CAC TAC Met Phe Cys Leu Ser Pro Thr Asn Leu Leu Arg Arg Phe Cys His Tyr 1130 1135 1140 1145	3578
ATC GTG ACC ATG AGG TAC TTC GAG GTG GTC ATT CTC GTG GTC ATC GCC Ile Val Thr Met Arg Tyr Phe Glu Val Val Ile Leu Val Val Ile Ala 1150 1155 1160	3626
TTG AGC AGC ATC GCC CTG GCT GCT GAG GAC CCA GTG CGC ACA GAC TCG Leu Ser Ser Ile Ala Leu Ala Ala Glu Asp Pro Val Arg Thr Asp Ser 1165 1170 1175	3674
CCC AGG AAC AAC GCT CTG AAA TAC CTG GAT TAC ATT TTC ACT GGT GTC Pro Arg Asn Asn Ala Leu Lys Tyr Leu Asp Tyr Ile Phe Thr Gly Val 1180 1185 1190	3722

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TTT ACC TTT GAG ATG GTG ATA AAG ATG ATC GAC TTG GGA CTG CTG CTT	3770
Phe Thr Phe Glu Met Val Ile Lys Met Ile Asp Leu Gly Leu Leu Leu	
1195 1200 1205	
CAC CCT GGA GCC TAT TTC CGG GAC TTG TGG AAC ATT CTG GAC TTC ATT	3818
His Pro Gly Ala Tyr Phe Arg Asp Leu Trp Asn Ile Leu Asp Phe Ile	
1210 1215 1220 1225	
GTG GTC AGT GGC GCC CTG GTG GCG TTT GCT TTC TCA GGA TCC AAA GGG	3866
Val Val Ser Gly Ala Leu Val Ala Phe Ala Phe Ser Gly Ser Lys Gly	
1230 1235 1240	
AAA GAC ATC AAT ACC ATC AAG TCT CTG AGA GTC CTT CGT GTC CTG CGG	3914
Lys Asp Ile Asn Thr Ile Lys Ser Leu Arg Val Leu Arg Val Leu Arg	
1245 1250 1255	
CCC CTC AAG ACC ATC AAA CGG CTG CCC AAG CTC AAG GCT GTG TTT GAC	3962
Pro Leu Lys Thr Ile Lys Arg Leu Pro Lys Leu Lys Ala Val Phe Asp	
1260 1265 1270	
TGT GTG GTG AAC TCC CTG AAG AAT GTC CTC AAC ATC TTG ATT GTC TAC	4010
Cys Val Val Asn Ser Leu Lys Asn Val Leu Asn Ile Leu Ile Val Tyr	
1275 1280 1285	
ATG CTC TTC ATG TTC ATA TTT GCC GTC ATT GCG GTG CAG CTC TTC AAA	4058
Met Leu Phe Met Phe Ile Phe Ala Val Ile Ala Val Gln Leu Phe Lys	
1290 1295 1300 1305	
GGG AAG TTT TTC TAC TGC ACA GAT GAA TCC AAG GAG CTG GAG AGG GAC	4106
Gly Lys Phe Phe Tyr Cys Thr Asp Glu Ser Lys Glu Leu Glu Arg Asp	
1310 1315 1320	
TGC AGG GGT CAG TAT TTG GAT TAT GAG AAG GAG GAA GTG GAA GCT CAG	4154
Cys Arg Gly Gln Tyr Leu Asp Tyr Glu Lys Glu Glu Val Glu Ala Gln	
1325 1330 1335	
CCC AGG CAG TGG AAG AAA TAC GAC TTT CAC TAC GAC AAT GTG CTC TGG	4202
Pro Arg Gln Trp Lys Lys Tyr Asp Phe His Tyr Asp Asn Val Leu Trp	
1340 1345 1350	
GCT CTG CTG ACG CTG TTC ACA GTG TCC ACG GGA GAA GGC TGG CCC ATG	4250
Ala Leu Leu Thr Leu Phe Thr Val Ser Thr Gly Glu Gly Trp Pro Met	
1355 1360 1365	
GTG CTG AAA CAC TCC GTG GAT GCC ACC TAT GAG GAG CAG GGT CCA AGC	4298
Val Leu Lys His Ser Val Asp Ala Thr Tyr Glu Glu Gln Gly Pro Ser	
1370 1375 1380 1385	
CCT GGG TAC CGC ATG GAG CTG TCC ATC TTC TAC GTG GTC TAC TTT GTG	4346
Pro Gly Tyr Arg Met Glu Leu Ser Ile Phe Tyr Val Val Tyr Phe Val	
1390 1395 1400	
GTC TTT CCC TTC TTC TTC GTC AAC ATC TTT GTG GCT TTG ATC ATC ATC	4394
Val Phe Pro Phe Phe Phe Val Asn Ile Phe Val Ala Leu Ile Ile Ile	
1405 1410 1415	

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ACC	TTC	CAG	GAG	CAG	GGG	GAC	AAG	GTG	ATG	TCT	GAA	TGC	AGC	CTG	GAG	4442
Thr	Phe	Gln	Glu	Gln	Gly	Asp	Lys	Val	Met	Ser	Glu	Cys	Ser	Leu	Glu	
		1420					1425					1430				
AAG	AAC	GAG	AGG	GCT	TGC	ATT	GAC	TTC	GCC	ATC	AGC	GCC	AAA	CCC	CTG	4490
Lys	Asn	Glu	Arg	Ala	Cys	Ile	Asp	Phe	Ala	Ile	Ser	Ala	Lys	Pro	Leu	
	1435					1440					1445					
ACA	CGG	TAC	ATG	CCC	CAA	AAC	CGG	CAG	TCG	TTC	CAG	TAT	AAG	ACG	TGG	4538
Thr	Arg	Tyr	Met	Pro	Gln	Asn	Arg	Gln	Ser	Phe	Gln	Tyr	Lys	Thr	Trp	
1450					1455				1460						1465	
ACA	TTT	GTG	GTC	TCC	CCG	CCC	TTT	GAA	TAC	TTC	ATC	ATG	GCC	ATG	ATA	4586
Thr	Phe	Val	Val	Ser	Pro	Pro	Phe	Glu	Tyr	Phe	Ile	Met	Ala	Met	Ile	
				1470					1475					1480		
GCC	CTC	AAC	ACT	GTG	GTG	CTG	ATG	ATG	AAG	TTC	TAT	GAT	GCA	CCC	TAT	4634
Ala	Leu	Asn	Thr	Val	Val	Leu	Met	Met	Lys	Phe	Tyr	Asp	Ala	Pro	Tyr	
			1485					1490					1495			
GAG	TAC	GAG	CTG	ATG	CTG	AAA	TGC	CTG	AAC	ATC	GTG	TTC	ACA	TCC	ATG	4682
Glu	Tyr	Glu	Leu	Met	Leu	Lys	Cys	Leu	Asn	Ile	Val	Phe	Thr	Ser	Met	
		1500					1505					1510				
TTC	TCC	ATG	GAA	TGC	GTG	CTG	AAG	ATC	ATC	GCC	TTT	GGG	GTG	CTG	AAC	4730
Phe	Ser	Met	Glu	Cys	Val	Leu	Lys	Ile	Ile	Ala	Phe	Gly	Val	Leu	Asn	
	1515					1520					1525					
TAT	TTC	AGA	GAT	GCC	TGG	AAT	GTC	TTT	GAC	TTT	GTC	ACT	GTG	TTG	GGA	4778
Tyr	Phe	Arg	Asp	Ala	Trp	Asn	Val	Phe	Asp	Phe	Val	Thr	Val	Leu	Gly	
1530					1535				1540						1545	
AGT	ATT	ACT	GAT	ATT	TTA	GTA	ACA	GAG	ATT	GCG	GAA	ACG	AAC	AAT	TTC	4826
Ser	Ile	Thr	Asp	Ile	Leu	Val	Thr	Glu	Ile	Ala	Glu	Thr	Asn	Asn	Phe	
				1550					1555					1560		
ATC	AAC	CTC	AGC	TTC	CTC	CGC	CTC	TTT	CGA	GCT	GCG	CGG	CTG	ATC	AAG	4874
Ile	Asn	Leu	Ser	Phe	Leu	Arg	Leu	Phe	Arg	Ala	Ala	Arg	Leu	Ile	Lys	
			1565					1570					1575			
CTG	CTC	CGC	CAG	GGC	TAC	ACC	ATC	CGC	ATC	CTG	CTG	TGG	ACC	TTT	GTC	4922
Leu	Leu	Arg	Gln	Gly	Tyr	Thr	Ile	Arg	Ile	Leu	Leu	Trp	Thr	Phe	Val	
		1580					1585					1590				
CAG	TCC	TTC	AAG	GCC	CTG	CCC	TAC	GTG	TGT	CTG	CTC	ATT	GCC	ATG	CTG	4970
Gln	Ser	Phe	Lys	Ala	Leu	Pro	Tyr	Val	Cys	Leu	Leu	Ile	Ala	Met	Leu	
	1595					1600					1605					
TTC	TTC	ATC	TAC	GCC	ATC	ATC	GGC	ATG	CAG	GTG	TTT	GGG	AAT	ATT	GCC	5018
Phe	Phe	Ile	Tyr	Ala	Ile	Ile	Gly	Met	Gln	Val	Phe	Gly	Asn	Ile	Ala	
1610					1615					1620					1625	
CTG	GAT	GAT	GAC	ACC	AGC	ATC	AAC	CGC	CAC	AAC	AAC	TTC	CGG	ACG	TTT	5066
Leu	Asp	Asp	Asp	Thr	Ser	Ile	Asn	Arg	His	Asn	Asn	Phe	Arg	Thr	Phe	
				1630					1635					1640		

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TTG CAA GCC CTG ATG CTG CTG TTC AGG AGC GCC ACG GGG GAG GCC TGG	5114
Leu Gln Ala Leu Met Leu Leu Phe Arg Ser Ala Thr Gly Glu Ala Trp	
1645 1650 1655	
CAC GAG ATC ATG CTG TCC TGC CTG AGC AAC CAG GCC TGT GAT GAG CAG	5162
His Glu Ile Met Leu Ser Cys Leu Ser Asn Gln Ala Cys Asp Glu Gln	
1660 1665 1670	
GCC AAT GCC ACC GAG TGT GGA AGT GAC TTT GCC TAC TTC TAC TTC GTC	5210
Ala Asn Ala Thr Glu Cys Gly Ser Asp Phe Ala Tyr Phe Tyr Phe Val	
1675 1680 1685	
TCC TTC ATC TTC CTG TGC TCC TTT CTG ATG TTG AAC CTC TTT GTG GCT	5258
Ser Phe Ile Phe Leu Cys Ser Phe Leu Met Leu Asn Leu Phe Val Ala	
1690 1695 1700 1705	
GTG ATC ATG GAC AAT TTT GAG TAC CTC ACG CGG GAC TCT TCC ATC CTA	5306
Val Ile Met Asp Asn Phe Glu Tyr Leu Thr Arg Asp Ser Ser Ile Leu	
1710 1715 1720	
GGT CCT CAC CAC TTG GAT GAG TTC ATC CGG GTC TGG GCT GAA TAC GAC	5354
Gly Pro His His Leu Asp Glu Phe Ile Arg Val Trp Ala Glu Tyr Asp	
1725 1730 1735	
CCG GCT GCG TGT GGG CGC ATC AGT TAC AAT GAC ATG TTT GAG ATG CTG	5402
Pro Ala Ala Cys Gly Arg Ile Ser Tyr Asn Asp Met Phe Glu Met Leu	
1740 1745 1750	
AAA CAC ATG TCC CCG CCT CTG GGG CTG GGG AAG AAA TGC CCT GCT CGA	5450
Lys His Met Ser Pro Pro Leu Gly Leu Gly Lys Lys Cys Pro Ala Arg	
1755 1760 1765	
GTT GCT TAC AAG CGC CTG GTT CGC ATG AAC ATG CCC ATC TCC AAC GAG	5498
Val Ala Tyr Lys Arg Leu Val Arg Met Asn Met Pro Ile Ser Asn Glu	
1770 1775 1780 1785	
GAC ATG ACT GTT CAC TTC ACG TCC ACG CTG ATG GCC CTC ATC CGG ACG	5546
Asp Met Thr Val His Phe Thr Ser Thr Leu Met Ala Leu Ile Arg Thr	
1790 1795 1800	
GCA CTG GAG ATC AAG CTG GCC CCA GCT GGG ACA AAG CAG CAT CAG TGT	5594
Ala Leu Glu Ile Lys Leu Ala Pro Ala Gly Thr Lys Gln His Gln Cys	
1805 1810 1815	
GAC GCG GAG TTG AGG AAG GAG ATT TCC GTT GTG TGG GCC AAT CTG CCC	5642
Asp Ala Glu Leu Arg Lys Glu Ile Ser Val Val Trp Ala Asn Leu Pro	
1820 1825 1830	
CAG AAG ACT TTG GAC TTG CTG GTA CCA CCC CAT AAG CCT GAT GAG ATG	5690
Gln Lys Thr Leu Asp Leu Leu Val Pro Pro His Lys Pro Asp Glu Met	
1835 1840 1845	
ACA GTG GGG AAG GTT TAT GCA GCT CTG ATG ATA TTT GAC TTC TAC AAG	5738
Thr Val Gly Lys Val Tyr Ala Ala Leu Met Ile Phe Asp Phe Tyr Lys	
1850 1855 1860 1865	

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CAG AAC AAA ACC ACC AGA GAC CAG ATG CAG CAG GCT CCT GGA GGC CTC Gln Asn Lys Thr Thr Arg Asp Gln Met Gln Gln Ala Pro Gly Gly Leu 1870 1875 1880	5786
TCC CAG ATG GGT CCT GTG TCC CTG TTC CAC CCT CTG AAG GCC ACC CTG Ser Gln Met Gly Pro Val Ser Leu Phe His Pro Leu Lys Ala Thr Leu 1885 1890 1895	5834
GAG CAG ACA CAG CCG GCT GTG CTC CGA GGA GCC CGG GTT TTC CTT CGA Glu Gln Thr Gln Pro Ala Val Leu Arg Gly Ala Arg Val Phe Leu Arg 1900 1905 1910	5882
CAG AAG AGT TCC ACC TCC CTC AGC AAT GGC GGG GCC ATA CAA AAC CAA Gln Lys Ser Ser Thr Ser Leu Ser Asn Gly Gly Ala Ile Gln Asn Gln 1915 1920 1925	5930
GAG AGT GGC ATC AAA GAG TCT GTC TCC TGG GGC ACT CAA AGG ACC CAG Glu Ser Gly Ile Lys Glu Ser Val Ser Trp Gly Thr Gln Arg Thr Gln 1930 1935 1940 1945	5978
GAT GCA CCC CAT GAG GCC AGG CCA CCC CTG GAG CGT GGC CAC TCC ACA Asp Ala Pro His Glu Ala Arg Pro Pro Leu Glu Arg Gly His Ser Thr 1950 1955 1960	6026
GAG ATC CCT GTG GGG CGG TCA GGA GCA CTG GCT GTG GAC GTT CAG ATG Glu Ile Pro Val Gly Arg Ser Gly Ala Leu Ala Val Asp Val Gln Met 1965 1970 1975	6074
CAG AGC ATA ACC CGG AGG GGC CCT GAT GGG GAG CCC CAG CCT GGG CTG Gln Ser Ile Thr Arg Arg Gly Pro Asp Gly Glu Pro Gln Pro Gly Leu 1980 1985 1990	6122
GAG AGC CAG GGT CGA GCG GCC TCC ATG CCC CGC CTT GCG GCC GAG ACT Glu Ser Gln Gly Arg Ala Ala Ser Met Pro Arg Leu Ala Ala Glu Thr 1995 2000 2005	6170
CAG CCC GTC ACA GAT GCC AGC CCC ATG AAG CGC TCC ATC TCC ACG CTG Gln Pro Val Thr Asp Ala Ser Pro Met Lys Arg Ser Ile Ser Thr Leu 2010 2015 2020 2025	6218
GCC CAG CGG CCC CGT GGG ACT CAT CTT TGC AGC ACC ACC CCG GAC CGC Ala Gln Arg Pro Arg Gly Thr His Leu Cys Ser Thr Thr Pro Asp Arg 2030 2035 2040	6266
CCA CCC CCT AGC CAG GCG TCG TCG CAC CAC CAC CAC CAC CGC TGC CAC Pro Pro Pro Ser Gln Ala Ser Ser His His His His His Arg Cys His 2045 2050 2055	6314
CGC CGC AGG GAC AGG AAG CAG AGG TCC CTG GAG AAG GGG CCC AGC CTG Arg Arg Arg Asp Arg Lys Gln Arg Ser Leu Glu Lys Gly Pro Ser Leu 2060 2065 2070	6362
TCT GCC GAT ATG GAT GGC GCA CCA AGC AGT GCT GTG GGG CCG GGG CTG Ser Ala Asp Met Asp Gly Ala Pro Ser Ser Ala Val Gly Pro Gly Leu 2075 2080 2085	6410

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CCC CCG GGA GAG GGG CCT ACA GGC TGC CGG CGG GAA CGA GAG CGC CGG Pro Pro Gly Glu Gly Pro Thr Gly Cys Arg Arg Glu Arg Glu Arg Arg 2090 2095 2100 2105	6458
CAG GAG CGG GGC CGG TCC CAG GAG CGG AGG CAG CCC TCA TCC TCC TCC Gln Glu Arg Gly Arg Ser Gln Glu Arg Arg Gln Pro Ser Ser Ser Ser 2110 2115 2120	6506
TCG GAG AAG CAG CGC TTC TAC TCC TGC GAC CGC TTT GGG GGC CGT GAG Ser Glu Lys Gln Arg Phe Tyr Ser Cys Asp Arg Phe Gly Gly Arg Glu 2125 2130 2135	6554
CCC CCG AAG CCC AAG CCC TCC CTC AGC AGC CAC CCA ACG TCG CCA ACA Pro Pro Lys Pro Lys Pro Ser Leu Ser Ser His Pro Thr Ser Pro Thr 2140 2145 2150	6602
GCT GGC CAG GAG CCG GGA CCC CAC CCA CAG GGC AGT GGT TCC GTG AAT Ala Gly Gln Glu Pro Gly Pro His Pro Gln Gly Ser Gly Ser Val Asn 2155 2160 2165	6650
GGG AGC CCC TTG CTG TCA ACA TCT GGT GCT AGC ACC CCC GGC CGC GGT Gly Ser Pro Leu Leu Ser Thr Ser Gly Ala Ser Thr Pro Gly Arg Gly 2170 2175 2180 2185	6698
GGG CGG AGG CAG CTC CCC CAG ACG CCC CTG ACT CCC CGC CCC AGC ATC Gly Arg Arg Gln Leu Pro Gln Thr Pro Leu Thr Pro Arg Pro Ser Ile 2190 2195 2200	6746
ACC TAC AAG ACG GCC AAC TCC TCA CCC ATC CAC TTC GCC GGG GCT CAG Thr Tyr Lys Thr Ala Asn Ser Ser Pro Ile His Phe Ala Gly Ala Gln 2205 2210 2215	6794
ACC AGC CTC CCT GCC TTC TCC CCA GGC CGG CTC AGC CGT GGG CTT TCC Thr Ser Leu Pro Ala Phe Ser Pro Gly Arg Leu Ser Arg Gly Leu Ser 2220 2225 2230	6842
GAA CAC AAC GCC CTG CTG CAG AGA GAC CCC CTC AGC CAG CCC CTG GCC Glu His Asn Ala Leu Leu Gln Arg Asp Pro Leu Ser Gln Pro Leu Ala 2235 2240 2245	6890
CCT GGC TCT CGA ATT GGC TCT GAC CCT TAC CTG GGG CAG CGT CTG GAC Pro Gly Ser Arg Ile Gly Ser Asp Pro Tyr Leu Gly Gln Arg Leu Asp 2250 2255 2260 2265	6938
AGT GAG GCC TCT GTC CAC GCC CTG CCT GAG GAC ACG CTC ACT TTC GAG Ser Glu Ala Ser Val His Ala Leu Pro Glu Asp Thr Leu Thr Phe Glu 2270 2275 2280	6986
GAG GCT GTG GCC ACC AAC TCG GGC CGC TCC TCC AGG ACT TCC TAC GTG Glu Ala Val Ala Thr Asn Ser Gly Arg Ser Ser Arg Thr Ser Tyr Val 2285 2290 2295	7034
TCC TCC CTG ACC TCC CAG TCT CAC CCT CTC CGC CGC GTG CCC AAC GGT Ser Ser Leu Thr Ser Gln Ser His Pro Leu Arg Arg Val Pro Asn Gly 2300 2305 2310	7082

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TAC CAC TGC ACC CTG GGA CTC AGC TCG GGT GGC CGA GCA CGG CAC AGC 7130
 Tyr His Cys Thr Leu Gly Leu Ser Ser Gly Gly Arg Ala Arg His Ser
 2315 2320 2325

TAC CAC CAC CCT GAC CAA GAC CAC TGG TGC TAGCTGCACC GTGACCGCTC 7180
 Tyr His His Pro Asp Gln Asp His Trp Cys
 2330 2335 234

AGACGCCTGC ATGCAGCAGG CGTGTGTTCC AGTGGATGAG TTTTATCATC CACACGGGGC 7240

AGTCGGCCCT CGGGGGAGGC CTTGCCCACC TTGGTGAGGC TCCTGTGGCC CCTCCCTCCC 7300

CCTCCTCCCC TCTTTTACTC TAGACGACGA ATAAAGCCCT GTTGCTTGAG TGTACGTACC 7360

GC 7362

(2) INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 7175 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 144..6857

- (ix) FEATURE:
 (A) NAME/KEY: 5'UTR
 (B) LOCATION: 1..143

- (ix) FEATURE:
 (A) NAME/KEY: 3'UTR
 (B) LOCATION: 6855..7175

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GCGGCGGCGG CTGCGGCGGT GGGGCCGGGC GAGGTCCGTG CGGTCCCGGC GGCTCCGTGG 60

CTGCTCCGCT CTGAGCGCCT GCGCGCCCCG CGCCCTCCCT GCCGGGGCCG CTGGGCCGGG 120

GATGCACGCG GGGCCCGGGA GCC ATG GTC CGC TTC GGG GAC GAG CTG GGC 170
 Met Val Arg Phe Gly Asp Glu Leu Gly
 1 5

GGC CGC TAT GGA GGC CCC GGC GGC GGA GAG CGG GCC CGG GGC GGC GGG 218
 Gly Arg Tyr Gly Gly Pro Gly Gly Gly Glu Arg Ala Arg Gly Gly Gly
 10 15 20 25

GCC GGC GGG GCG GGG GGC CCG GGT CCC GGG GGG CTG CAG CCC GGC CAG 266
 Ala Gly Gly Ala Gly Gly Pro Gly Pro Gly Gly Leu Gln Pro Gly Gln
 30 35 40

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CGG	GTC	CTC	TAC	AAG	CAA	TCG	ATC	GCG	CAG	CGC	GCG	CGG	ACC	ATG	GCG	314
Arg	Val	Leu	Tyr	Lys	Gln	Ser	Ile	Ala	Gln	Arg	Ala	Arg	Thr	Met	Ala	
			45					50					55			
CTG	TAC	AAC	CCC	ATC	CCG	GTC	AAG	CAG	AAC	TGC	TTC	ACC	GTC	AAC	CGC	362
Leu	Tyr	Asn	Pro	Ile	Pro	Val	Lys	Gln	Asn	Cys	Phe	Thr	Val	Asn	Arg	
		60					65					70				
TCG	CTC	TTC	GTC	TTC	AGC	GAG	GAC	AAC	GTC	GTC	CGC	AAA	TAC	GCG	AAG	410
Ser	Leu	Phe	Val	Phe	Ser	Glu	Asp	Asn	Val	Val	Arg	Lys	Tyr	Ala	Lys	
	75					80					85					
CGC	ATC	ACC	GAG	TGG	CCT	CCA	TTC	GAG	AAT	ATG	ATC	CTG	GCC	ACC	ATC	458
Arg	Ile	Thr	Glu	Trp	Pro	Pro	Phe	Glu	Asn	Met	Ile	Leu	Ala	Thr	Ile	
	90				95					100					105	
ATC	GCC	AAC	TGC	ATC	GTG	CTG	GCC	CTG	GAG	CAG	CAC	CTC	CCT	GAT	GGG	506
Ile	Ala	Asn	Cys	Ile	Val	Leu	Ala	Leu	Glu	Gln	His	Leu	Pro	Asp	Gly	
				110					115					120		
GAC	AAA	ACG	CCC	ATG	TCC	GAG	CGG	CTG	GAC	GAC	ACG	GAG	CCC	TAT	TTC	554
Asp	Lys	Thr	Pro	Met	Ser	Glu	Arg	Leu	Asp	Asp	Thr	Glu	Pro	Tyr	Phe	
			125					130					135			
ATC	GGG	ATC	TTT	TGC	TTC	GAG	GCA	GGG	ATC	AAA	ATC	ATC	GCT	CTG	GGC	602
Ile	Gly	Ile	Phe	Cys	Phe	Glu	Ala	Gly	Ile	Lys	Ile	Ile	Ala	Leu	Gly	
		140					145					150				
TTT	GTC	TTC	CAC	AAG	GGC	TCT	TAC	CTG	CGG	AAC	GGC	TGG	AAC	GTC	ATG	650
Phe	Val	Phe	His	Lys	Gly	Ser	Tyr	Leu	Arg	Asn	Gly	Trp	Asn	Val	Met	
	155					160					165					
GAC	TTC	GTG	GTC	GTC	CTC	ACA	GGG	ATC	CTT	GCC	ACG	GCT	GGA	ACT	GAC	698
Asp	Phe	Val	Val	Val	Leu	Thr	Gly	Ile	Leu	Ala	Thr	Ala	Gly	Thr	Asp	
	170				175					180					185	
TTC	GAC	CTG	CGA	ACA	CTG	AGG	GCT	GTG	CGT	GTG	CTG	AGG	CCC	CTG	AAG	746
Phe	Asp	Leu	Arg	Thr	Leu	Arg	Ala	Val	Arg	Val	Leu	Arg	Pro	Leu	Lys	
				190					195					200		
CTG	GTG	TCT	GGG	ATT	CCA	AGT	TTG	CAG	GTG	GTG	CTC	AAG	TCC	ATC	ATG	794
Leu	Val	Ser	Gly	Ile	Pro	Ser	Leu	Gln	Val	Val	Leu	Lys	Ser	Ile	Met	
			205					210					215			
AAG	GCC	ATG	GTT	CCA	CTC	CTG	CAG	ATT	GGG	CTG	CTT	CTC	TTC	TTT	GCC	842
Lys	Ala	Met	Val	Pro	Leu	Leu	Gln	Ile	Gly	Leu	Leu	Leu	Phe	Phe	Ala	
		220					225					230				
ATC	CTC	ATG	TTT	GCC	ATC	ATT	GGC	CTG	GAG	TTC	TAC	ATG	GGC	AAG	TTC	890
Ile	Leu	Met	Phe	Ala	Ile	Ile	Gly	Leu	Glu	Phe	Tyr	Met	Gly	Lys	Phe	
	235					240					245					
CAC	AAG	GCC	TGT	TTC	CCC	AAC	AGC	ACA	GAT	GCG	GAG	CCC	GTG	GGT	GAC	938
His	Lys	Ala	Cys	Phe	Pro	Asn	Ser	Thr	Asp	Ala	Glu	Pro	Val	Gly	Asp	
					255					260					265	

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TTC	CCC	TGT	GGC	AAG	GAG	GCC	CCA	GCC	CGG	CTG	TGC	GAG	GGC	GAC	ACT	986
Phe	Pro	Cys	Gly	Lys	Glu	Ala	Pro	Ala	Arg	Leu	Cys	Glu	Gly	Asp	Thr	
				270					275					280		
GAG	TGC	CGG	GAG	TAC	TGG	CCA	GGA	CCC	AAC	TTT	GGC	ATC	ACC	AAC	TTT	1034
Glu	Cys	Arg	Glu	Tyr	Trp	Pro	Gly	Pro	Asn	Phe	Gly	Ile	Thr	Asn	Phe	
			285					290					295			
GAC	AAT	ATC	CTG	TTT	GCC	ATC	TTG	ACG	GTG	TTC	CAG	TGC	ATC	ACC	ATG	1082
Asp	Asn	Ile	Leu	Phe	Ala	Ile	Leu	Thr	Val	Phe	Gln	Cys	Ile	Thr	Met	
		300					305					310				
GAG	GGC	TGG	ACT	GAC	ATC	CTC	TAT	AAT	ACA	AAC	GAT	GCG	GCC	GGC	AAC	1130
Glu	Gly	Trp	Thr	Asp	Ile	Leu	Tyr	Asn	Thr	Asn	Asp	Ala	Ala	Gly	Asn	
	315					320					325					
ACC	TGG	AAC	TGG	CTC	TAC	TTC	ATC	CCT	CTC	ATC	ATC	ATC	GGC	TCC	TTC	1178
Thr	Trp	Asn	Trp	Leu	Tyr	Phe	Ile	Pro	Leu	Ile	Ile	Ile	Gly	Ser	Phe	
	330				335					340					345	
TTC	ATG	CTC	AAC	CTG	GTG	CTG	GGC	GTG	CTC	TCG	GGG	GAG	TTT	GCC	AAG	1226
Phe	Met	Leu	Asn	Leu	Val	Leu	Gly	Val	Leu	Ser	Gly	Glu	Phe	Ala	Lys	
			350					355						360		
GAG	CGA	GAG	AGG	GTG	GAG	AAC	CGC	CGC	GCC	TTC	CTG	AAG	CTG	CGC	CGG	1274
Glu	Arg	Glu	Arg	Val	Glu	Asn	Arg	Arg	Ala	Phe	Leu	Lys	Leu	Arg	Arg	
			365					370					375			
CAG	CAG	CAG	ATC	GAG	CGA	GAG	CTC	AAC	GGG	TAC	CTG	GAG	TGG	ATC	TTC	1322
Gln	Gln	Gln	Ile	Glu	Arg	Glu	Leu	Asn	Gly	Tyr	Leu	Glu	Trp	Ile	Phe	
		380					385					390				
AAG	GCG	GAG	GAA	GTC	ATG	CTG	GCC	GAG	GAG	GAC	AGG	AAT	GCA	GAG	GAG	1370
Lys	Ala	Glu	Glu	Val	Met	Leu	Ala	Glu	Glu	Asp	Arg	Asn	Ala	Glu	Glu	
	395					400					405					
AAG	TCC	CCT	TTG	GAC	GTG	CTG	AAG	AGA	GCG	GCC	ACC	AAG	AAG	AGC	AGA	1418
Lys	Ser	Pro	Leu	Asp	Val	Leu	Lys	Arg	Ala	Ala	Thr	Lys	Lys	Ser	Arg	
	410				415					420				425		
AAT	GAC	CTG	ATC	CAC	GCA	GAG	GAG	GGA	GAG	GAC	CGG	TTT	GCA	GAT	CTC	1466
Asn	Asp	Leu	Ile	His	Ala	Glu	Glu	Gly	Glu	Asp	Arg	Phe	Ala	Asp	Leu	
				430				435					440			
TGT	GCT	GTT	GGA	TCC	CCC	TTC	GCC	CGC	GCC	AGC	CTC	AAG	AGC	GGG	AAG	1514
Cys	Ala	Val	Gly	Ser	Pro	Phe	Ala	Arg	Ala	Ser	Leu	Lys	Ser	Gly	Lys	
			445					450					455			
ACA	GAG	AGC	TCG	TCA	TAC	TTC	CGG	AGG	AAG	GAG	AAG	ATG	TTC	CGG	TTT	1562
Thr	Glu	Ser	Ser	Ser	Tyr	Phe	Arg	Arg	Lys	Glu	Lys	Met	Phe	Arg	Phe	
		460					465					470				
TTT	ATC	CGG	CGC	ATG	GTG	AAG	GCT	CAG	AGC	TTC	TAC	TGG	GTG	GTG	CTG	1610
Phe	Ile	Arg	Arg	Met	Val	Lys	Ala	Gln	Ser	Phe	Tyr	Trp	Val	Val	Leu	
	475					480					485					

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TGC Cys 490	GTG Val	GTG Val	GCC Ala	CTG Leu	AAC Asn 495	ACA Thr	CTG Leu	TGT Cys	GTG Val	GCC Ala 500	ATG Met	GTG Val	CAT His	TAC Tyr	AAC Asn 505	1658
CAG Gln	CCG Pro	CGG Arg	CGG Arg	CTT Leu 510	ACC Thr	ACG Thr	ACC Thr	CTG Leu	TAT Tyr 515	TTT Phe	GCA Ala	GAG Glu	TTT Phe	GTT Val 520	TTC Phe	1706
CTG Leu	GGT Gly	CTC Leu	TTC Phe 525	CTC Leu	ACA Thr	GAG Glu	ATG Met	TCC Ser 530	CTG Leu	AAG Lys	ATG Met	TAT Tyr	GGC Gly 535	CTG Leu	GGG Gly	1754
CCC Pro	AGA Arg	AGC Ser 540	TAC Tyr	TTC Phe	CGG Arg	TCC Ser 545	TCC Ser	TTC Phe	AAC Asn	TGC Cys	TTC Phe	GAC Asp 550	TTT Phe	GGG Gly	GTC Val	1802
ATC Ile	GTG Val 555	GGG Gly	AGC Ser	GTC Val	TTT Phe	GAA Glu 560	GTG Val	GTC Val	TGG Trp	GCG Ala	GCC Ala 565	ATC Ile	AAG Lys	CCG Pro	GGA Gly	1850
AGC Ser 570	TCC Ser	TTT Phe	GGG Gly	ATC Ile	AGT Ser 575	GTG Val	CTG Leu	CGG Arg	GCC Ala	CTC Leu 580	CGC Arg	CTG Leu	CTG Leu	AGG Arg	ATC Ile 585	1898
TTC Phe	AAA Lys	GTC Val	ACG Thr	AAG Lys 590	TAC Tyr	TGG Trp	AGC Ser	TCC Ser	CTG Leu 595	CGG Arg	AAC Asn	CTG Leu	GTG Val	GTG Val	TCC Ser	1946
CTG Leu	CTG Leu	AAC Asn 605	TCC Ser	ATG Met	AAG Lys	TCC Ser	ATC Ile	ATC Ile 610	AGC Ser	CTG Leu	CTC Leu	TTC Phe	TTG Leu 615	CTC Leu	TTC Phe	1994
CTG Leu	TTC Phe 620	ATT Ile	GTG Val	GTC Val	TTC Phe	GCC Ala	CTG Leu 625	CTG Leu	GGG Gly	ATG Met	CAG Gln	CTG Leu 630	TTT Phe	GGG Gly	GGA Gly	2042
CAG Gln 635	TTC Phe	AAC Asn	TTC Phe	CAG Gln	GAT Asp	GAG Glu 640	ACT Thr	CCC Pro	ACA Thr	ACC Thr	AAC Asn 645	TTC Phe	GAC Asp	ACC Thr	TTC Phe	2090
CCT Pro 650	GCC Ala	GCC Ala	ATC Ile	CTC Leu	ACT Thr 655	GTC Val	TTC Phe	CAG Gln	ATC Ile	CTG Leu 660	ACG Thr	GGA Gly	GAG Glu	GAC Asp	TGG Trp 665	2138
AAT Asn	GCA Ala	GTG Val	ATG Met	TAT Tyr 670	CAC His	GGG Gly	ATC Ile	GAA Glu	TCG Ser 675	CAA Gln	GGC Gly	GGC Gly	GTC Val	AGC Ser 680	AAA Lys	2186
GGC Gly	ATG Met	TTC Phe	TCG Ser	TCC Ser	TTT Phe	TAC Tyr	TTC Phe	ATT Ile 690	GTC Val	CTG Leu	ACA Thr	CTG Leu	TTC Phe 695	GGA Gly	AAC Asn	2234
TAC Tyr	ACT Thr	CTG Leu 700	CTG Leu	AAT Asn	GTC Val	TTT Phe	CTG Leu 705	GCC Ala	ATC Ile	GCT Ala	GTG Val	GAC Asp	AAC Asn	CTG Leu	GCC Ala	2282

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AAC	GCC	CAA	GAG	CTG	ACC	AAG	GAT	GAA	GAG	GAG	ATG	GAA	GAA	GCA	GCC	2330
Asn	Ala	Gln	Glu	Leu	Thr	Lys	Asp	Glu	Glu	Glu	Met	Glu	Glu	Ala	Ala	
715						720					725					
AAT	CAG	AAG	CTT	GCT	CTG	CAA	AAG	GCC	AAA	GAA	GTG	GCT	GAA	GTC	AGC	2378
Asn	Gln	Lys	Leu	Ala	Leu	Gln	Lys	Ala	Lys	Glu	Val	Ala	Glu	Val	Ser	
730					735					740					745	
CCC	ATG	TCT	GCC	GCG	AAC	ATC	TCC	ATC	GCC	GCC	AGG	CAG	CAG	AAC	TCG	2426
Pro	Met	Ser	Ala	Ala	Asn	Ile	Ser	Ile	Ala	Ala	Arg	Gln	Gln	Asn	Ser	
				750					755					760		
GCC	AAG	GCG	CGC	TCG	GTG	TGG	GAG	CAG	CGG	GCC	AGC	CAG	CTA	CGG	CTG	2474
Ala	Lys	Ala	Arg	Ser	Val	Trp	Glu	Gln	Arg	Ala	Ser	Gln	Leu	Arg	Leu	
			765					770					775			
CAG	AAC	CTG	CGG	GCC	AGC	TGC	GAG	GCG	CTG	TAC	AGC	GAG	ATG	GAC	CCC	2522
Gln	Asn	Leu	Arg	Ala	Ser	Cys	Glu	Ala	Leu	Tyr	Ser	Glu	Met	Asp	Pro	
		780					785					790				
GAG	GAG	CGG	CTG	CGC	TTC	GCC	ACT	ACG	CGC	CAC	CTG	CGG	CCC	GAC	ATG	2570
Glu	Glu	Arg	Leu	Arg	Phe	Ala	Thr	Thr	Arg	His	Leu	Arg	Pro	Asp	Met	
	795					800					805					
AAG	ACG	CAC	CTG	GAC	CGG	CCG	CTG	GTG	GTG	GAG	CTG	GGC	CGC	GAC	GGC	2618
Lys	Thr	His	Leu	Asp	Arg	Pro	Leu	Val	Val	Glu	Leu	Gly	Arg	Asp	Gly	
810					815					820					825	
GCG	CGG	GGG	CCC	GTG	GGA	GGC	AAA	GCC	CGA	CCT	GAG	GCT	GCG	GAG	GCC	2666
Ala	Arg	Gly	Pro	Val	Gly	Gly	Lys	Ala	Arg	Pro	Glu	Ala	Ala	Glu	Ala	
				830					835					840		
CCC	GAG	GGC	GTC	GAC	CCT	CCG	CGC	AGG	CAC	CAC	CGG	CAC	CGC	GAC	AAG	2714
Pro	Glu	Gly	Val	Asp	Pro	Pro	Arg	Arg	His	His	Arg	His	Arg	Asp	Lys	
			845					850					855			
GAC	AAG	ACC	CCC	GCG	GCG	GGG	GAC	CAG	GAC	CGA	GCA	GAG	GCC	CCG	AAG	2762
Asp	Lys	Thr	Pro	Ala	Ala	Gly	Asp	Gln	Asp	Arg	Ala	Glu	Ala	Pro	Lys	
		860					865					870				
GCG	GAG	AGC	GGG	GAG	CCC	GGT	GCC	CGG	GAG	GAG	CGG	CCG	CGG	CCG	CAC	2810
Ala	Glu	Ser	Gly	Glu	Pro	Gly	Ala	Arg	Glu	Glu	Arg	Pro	Arg	Pro	His	
	875					880					885					
CGC	AGC	CAC	AGC	AAG	GAG	GCC	GCG	GGG	CCC	CCG	GAG	GCG	CGG	AGC	GAG	2858
Arg	Ser	His	Ser	Lys	Glu	Ala	Ala	Gly	Pro	Pro	Glu	Ala	Arg	Ser	Glu	
890					895				900						905	
CGC	GGC	CGA	GGC	CCA	GGC	CCC	GAG	GGC	GGC	CGG	CGG	CAC	CAC	CGG	CGC	2906
Arg	Gly	Arg	Gly	Pro	Gly	Pro	Glu	Gly	Gly	Arg	Arg	His	His	Arg	Arg	
				910				915						920		
GGC	TCC	CCG	GAG	GAG	GCG	GCC	GAG	CGG	GAG	CCC	CGA	CGC	CAC	CGC	GCG	2954
Gly	Ser	Pro	Glu	Glu	Ala	Ala	Glu	Arg	Glu	Pro	Arg	Arg	His	Arg	Ala	
			925					930					935			

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CAC	CGG	CAC	CAG	GAT	CCG	AGC	AAG	GAG	TGC	GCC	GGC	GCC	AAG	GGC	GAG	3002
His	Arg	His	Gln	Asp	Pro	Ser	Lys	Glu	Cys	Ala	Gly	Ala	Lys	Gly	Glu	
		940					945					950				
CGG	CGC	GCG	CGG	CAC	CGC	GGC	GGC	CCC	CGA	GCG	GGG	CCC	CGG	GAG	GCG	3050
Arg	Arg	Ala	Arg	His	Arg	Gly	Gly	Pro	Arg	Ala	Gly	Pro	Arg	Glu	Ala	
	955					960					965					
GAG	AGC	GGG	GAG	GAG	CCG	GCG	CGG	CGG	CAC	CGG	GCC	CGG	CAC	AAG	GCG	3098
Glu	Ser	Gly	Glu	Glu	Pro	Ala	Arg	Arg	His	Arg	Ala	Arg	His	Lys	Ala	
970					975					980					985	
CAG	CCT	GCT	CAC	GAG	GCT	GTG	GAG	AAG	GAG	ACC	ACG	GAG	AAG	GAG	GCC	3146
Gln	Pro	Ala	His	Glu	Ala	Val	Glu	Lys	Glu	Thr	Thr	Glu	Lys	Glu	Ala	
			990					995						1000		
ACG	GAG	AAG	GAG	GCT	GAG	ATA	GTG	GAA	GCC	GAC	AAG	GAA	AAG	GAG	CTC	3194
Thr	Glu	Lys	Glu	Ala	Glu	Ile	Val	Glu	Ala	Asp	Lys	Glu	Lys	Glu	Leu	
		1005					1010						1015			
CGG	AAC	CAC	CAG	CCC	CGG	GAG	CCA	CAC	TGT	GAC	CTG	GAG	ACC	AGT	GGG	3242
Arg	Asn	His	Gln	Pro	Arg	Glu	Pro	His	Cys	Asp	Leu	Glu	Thr	Ser	Gly	
	1020					1025						1030				
ACT	GTG	ACT	GTG	GGT	CCC	ATG	CAC	ACA	CTG	CCC	AGC	ACC	TGT	CTC	CAG	3290
Thr	Val	Thr	Val	Gly	Pro	Met	His	Thr	Leu	Pro	Ser	Thr	Cys	Leu	Gln	
	1035				1040						1045					
AAG	GTG	GAG	GAA	CAG	CCA	GAG	GAT	GCA	GAC	AAT	CAG	CGG	AAC	GTC	ACT	3338
Lys	Val	Glu	Glu	Gln	Pro	Glu	Asp	Ala	Asp	Asn	Gln	Arg	Asn	Val	Thr	
1050				1055						1060				1065		
CGC	ATG	GGC	AGT	CAG	CCC	CCA	GAC	CCG	AAC	ACT	ATT	GTA	CAT	ATC	CCA	3386
Arg	Met	Gly	Ser	Gln	Pro	Pro	Asp	Pro	Asn	Thr	Ile	Val	His	Ile	Pro	
			1070					1075					1080			
GTG	ATG	CTG	ACG	GGC	CCT	CTT	GGG	GAA	GCC	ACG	GTC	GTT	CCC	AGT	GGT	3434
Val	Met	Leu	Thr	Gly	Pro	Leu	Gly	Glu	Ala	Thr	Val	Val	Pro	Ser	Gly	
		1085					1090					1095				
AAC	GTG	GAC	CTG	GAA	AGC	CAA	GCA	GAG	GGG	AAG	AAG	GAG	GTG	GAA	GCG	3482
Asn	Val	Asp	Leu	Glu	Ser	Gln	Ala	Glu	Gly	Lys	Lys	Glu	Val	Glu	Ala	
	1100						1105					1110				
GAT	GAC	GTG	ATG	AGG	AGC	GGC	CCC	CGG	CCT	ATC	GTC	CCA	TAC	AGC	TCC	3530
Asp	Asp	Val	Met	Arg	Ser	Gly	Pro	Arg	Pro	Ile	Val	Pro	Tyr	Ser	Ser	
	1115					1120					1125					
ATG	TTC	TGT	TTA	AGC	CCC	ACC	AAC	CTG	CTC	CGC	CGC	TTC	TGC	CAC	TAC	3578
Met	Phe	Cys	Leu	Ser	Pro	Thr	Asn	Leu	Leu	Arg	Arg	Phe	Cys	His	Tyr	
1130				1135				1140						1145		
ATC	GTG	ACC	ATG	AGG	TAC	TTC	GAG	GTG	GTC	ATT	CTC	GTG	GTC	ATC	GCC	3626
Ile	Val	Thr	Met	Arg	Tyr	Phe	Glu	Val	Val	Ile	Leu	Val	Val	Ile	Ala	
			1150					1155						1160		

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TTG AGC AGC ATC GCC CTG GCT GCT GAG GAC CCA GTG CGC ACA GAC TCG Leu Ser Ser Ile Ala Leu Ala Ala Glu Asp Pro Val Arg Thr Asp Ser 1165 1170 1175	3674
CCC AGG AAC AAC GCT CTG AAA TAC CTG GAT TAC ATT TTC ACT GGT GTC Pro Arg Asn Asn Ala Leu Lys Tyr Leu Asp Tyr Ile Phe Thr Gly Val 1180 1185 1190	3722
TTT ACC TTT GAG ATG GTG ATA AAG ATG ATC GAC TTG GGA CTG CTG CTT Phe Thr Phe Glu Met Val Ile Lys Met Ile Asp Leu Gly Leu Leu Leu 1195 1200 1205	3770
CAC CCT GGA GCC TAT TTC CGG GAC TTG TGG AAC ATT CTG GAC TTC ATT His Pro Gly Ala Tyr Phe Arg Asp Leu Trp Asn Ile Leu Asp Phe Ile 1210 1215 1220 1225	3818
GTG GTC AGT GGC GCC CTG GTG GCG TTT GCT TTC TCA GGA TCC AAA GGG Val Val Ser Gly Ala Leu Val Ala Phe Ala Phe Ser Gly Ser Lys Gly 1230 1235 1240	3866
AAA GAC ATC AAT ACC ATC AAG TCT CTG AGA GTC CTT CGT GTC CTG CGG Lys Asp Ile Asn Thr Ile Lys Ser Leu Arg Val Leu Arg Val Leu Arg 1245 1250 1255	3914
CCC CTC AAG ACC ATC AAA CGG CTG CCC AAG CTC AAG GCT GTG TTT GAC Pro Leu Lys Thr Ile Lys Arg Leu Pro Lys Leu Lys Ala Val Phe Asp 1260 1265 1270	3962
TGT GTG GTG AAC TCC CTG AAG AAT GTC CTC AAC ATC TTG ATT GTC TAC Cys Val Val Asn Ser Leu Lys Asn Val Leu Asn Ile Leu Ile Val Tyr 1275 1280 1285	4010
ATG CTC TTC ATG TTC ATA TTT GCC GTC ATT GCG GTG CAG CTC TTC AAA Met Leu Phe Met Phe Ile Phe Ala Val Ile Ala Val Gln Leu Phe Lys 1290 1295 1300 1305	4058
GGG AAG TTT TTC TAC TGC ACA GAT GAA TCC AAG GAG CTG GAG AGG GAC Gly Lys Phe Phe Tyr Cys Thr Asp Glu Ser Lys Glu Leu Glu Arg Asp 1310 1315 1320	4106
TGC AGG GGT CAG TAT TTG GAT TAT GAG AAG GAG GAA GTG GAA GCT CAG Cys Arg Gly Gln Tyr Leu Asp Tyr Glu Lys Glu Glu Val Glu Ala Gln 1325 1330 1335	4154
CCC AGG CAG TGG AAG AAA TAC GAC TTT CAC TAC GAC AAT GTG CTC TGG Pro Arg Gln Trp Lys Lys Tyr Asp Phe His Tyr Asp Asn Val Leu Trp 1340 1345 1350	4202
GCT CTG CTG ACG CTG TTC ACA GTG TCC ACG GGA GAA GGC TGG CCC ATG Ala Leu Leu Thr Leu Phe Thr Val Ser Thr Gly Glu Gly Trp Pro Met 1355 1360 1365	4250
GTG CTG AAA CAC TCC GTG GAT GCC ACC TAT GAG GAG CAG GGT CCA AGC Val Leu Lys His Ser Val Asp Ala Thr Tyr Glu Glu Gln Gly Pro Ser 1370 1375 1380 1385	4298

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CCT	GGG	TAC	CGC	ATG	GAG	CTG	TCC	ATC	TTC	TAC	GTG	GTC	TAC	TTT	GTG	4346
Pro	Gly	Tyr	Arg	Met	Glu	Leu	Ser	Ile	Phe	Tyr	Val	Val	Tyr	Phe	Val	
				1390					1395					1400		
GTC	TTT	CCC	TTC	TTC	TTC	GTC	AAC	ATC	TTT	GTG	GCT	TTG	ATC	ATC	ATC	4394
Val	Phe	Pro	Phe	Phe	Phe	Val	Asn	Ile	Phe	Val	Ala	Leu	Ile	Ile	Ile	
			1405					1410					1415			
ACC	TTC	CAG	GAG	CAG	GGG	GAC	AAG	GTG	ATG	TCT	GAA	TGC	AGC	CTG	GAG	4442
Thr	Phe	Gln	Glu	Gln	Gly	Asp	Lys	Val	Met	Ser	Glu	Cys	Ser	Leu	Glu	
		1420					1425					1430				
AAG	AAC	GAG	AGG	GCT	TGC	ATT	GAC	TTC	GCC	ATC	AGC	GCC	AAA	CCC	CTG	4490
Lys	Asn	Glu	Arg	Ala	Cys	Ile	Asp	Phe	Ala	Ile	Ser	Ala	Lys	Pro	Leu	
	1435					1440					1445					
ACA	CGG	TAC	ATG	CCC	CAA	AAC	CGG	CAG	TCG	TTC	CAG	TAT	AAG	ACG	TGG	4538
Thr	Arg	Tyr	Met	Pro	Gln	Asn	Arg	Gln	Ser	Phe	Gln	Tyr	Lys	Thr	Trp	
1450					1455				1460						1465	
ACA	TTT	GTG	GTC	TCC	CCG	CCC	TTT	GAA	TAC	TTC	ATC	ATG	GCC	ATG	ATA	4586
Thr	Phe	Val	Val	Ser	Pro	Pro	Phe	Glu	Tyr	Phe	Ile	Met	Ala	Met	Ile	
				1470				1475					1480			
GCC	CTC	AAC	ACT	GTG	GTG	CTG	ATG	ATG	AAG	TTC	TAT	GAT	GCA	CCC	TAT	4634
Ala	Leu	Asn	Thr	Val	Val	Leu	Met	Met	Lys	Phe	Tyr	Asp	Ala	Pro	Tyr	
			1485					1490					1495			
GAG	TAC	GAG	CTG	ATG	CTG	AAA	TGC	CTG	AAC	ATC	GTG	TTC	ACA	TCC	ATG	4682
Glu	Tyr	Glu	Leu	Met	Leu	Lys	Cys	Leu	Asn	Ile	Val	Phe	Thr	Ser	Met	
		1500					1505					1510				
TTC	TCC	ATG	GAA	TGC	GTG	CTG	AAG	ATC	ATC	GCC	TTT	GGG	GTG	CTG	AAC	4730
Phe	Ser	Met	Glu	Cys	Val	Leu	Lys	Ile	Ile	Ala	Phe	Gly	Val	Leu	Asn	
	1515					1520					1525					
TAT	TTC	AGA	GAT	GCC	TGG	AAT	GTC	TTT	GAC	TTT	GTC	ACT	GTG	TTG	GGA	4778
Tyr	Phe	Arg	Asp	Ala	Trp	Asn	Val	Phe	Asp	Phe	Val	Thr	Val	Leu	Gly	
1530					1535				1540					1545		
AGT	ATT	ACT	GAT	ATT	TTA	GTA	ACA	GAG	ATT	GCG	GAA	ACG	AAC	AAT	TTC	4826
Ser	Ile	Thr	Asp	Ile	Leu	Val	Thr	Glu	Ile	Ala	Glu	Thr	Asn	Asn	Phe	
				1550					1555					1560		
ATC	AAC	CTC	AGC	TTC	CTC	CGC	CTC	TTT	CGA	GCT	GCG	CGG	CTG	ATC	AAG	4874
Ile	Asn	Leu	Ser	Phe	Leu	Arg	Leu	Phe	Arg	Ala	Ala	Arg	Leu	Ile	Lys	
				1565				1570					1575			
CTG	CTC	CGC	CAG	GGC	TAC	ACC	ATC	CGC	ATC	CTG	CTG	TGG	ACC	TTT	GTC	4922
Leu	Leu	Arg	Gln	Gly	Tyr	Thr	Ile	Arg	Ile	Leu	Leu	Trp	Thr	Phe	Val	
		1580					1585					1590				
CAG	TCC	TTC	AAG	GCC	CTG	CCC	TAC	GTG	TGT	CTG	CTC	ATT	GCC	ATG	CTG	4970
Gln	Ser	Phe	Lys	Ala	Leu	Pro	Tyr	Val	Cys	Leu	Leu	Ile	Ala	Met	Leu	
	1595					1600					1605					

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TTC	TTC	ATC	TAC	GCC	ATC	ATC	GGC	ATG	CAG	GTG	TTT	GGG	AAT	ATT	GCC	5018
Phe	Phe	Ile	Tyr	Ala	Ile	Ile	Gly	Met	Gln	Val	Phe	Gly	Asn	Ile	Ala	
1610					1615					1620					1625	
CTG	GAT	GAT	GAC	ACC	AGC	ATC	AAC	CGC	CAC	AAC	AAC	TTC	CGG	ACG	TTT	5066
Leu	Asp	Asp	Asp	Thr	Ser	Ile	Asn	Arg	His	Asn	Asn	Phe	Arg	Thr	Phe	
				1630					1635					1640		
TTG	CAA	GCC	CTG	ATG	CTG	CTG	TTC	AGG	AGC	GCC	ACG	GGG	GAG	GCC	TGG	5114
Leu	Gln	Ala	Leu	Met	Leu	Leu	Phe	Arg	Ser	Ala	Thr	Gly	Glu	Ala	Trp	
			1645					1650					1655			
CAC	GAG	ATC	ATG	CTG	TCC	TGC	CTG	AGC	AAC	CAG	GCC	TGT	GAT	GAG	CAG	5162
His	Glu	Ile	Met	Leu	Ser	Cys	Leu	Ser	Asn	Gln	Ala	Cys	Asp	Glu	Gln	
		1660					1665					1670				
GCC	AAT	GCC	ACC	GAG	TGT	GGA	AGT	GAC	TTT	GCC	TAC	TTC	TAC	TTC	GTC	5210
Ala	Asn	Ala	Thr	Glu	Cys	Gly	Ser	Asp	Phe	Ala	Tyr	Phe	Tyr	Phe	Val	
	1675					1680					1685					
TCC	TTC	ATC	TTC	CTG	TGC	TCC	TTT	CTG	ATG	TTG	AAC	CTC	TTT	GTG	GCT	5258
Ser	Phe	Ile	Phe	Leu	Cys	Ser	Phe	Leu	Met	Leu	Asn	Leu	Phe	Val	Ala	
1690					1695					1700					1705	
GTG	ATC	ATG	GAC	AAT	TTT	GAG	TAC	CTC	ACG	CGG	GAC	TCT	TCC	ATC	CTA	5306
Val	Ile	Met	Asp	Asn	Phe	Glu	Tyr	Leu	Thr	Arg	Asp	Ser	Ser	Ile	Leu	
				1710					1715					1720		
GGT	CCT	CAC	CAC	TTG	GAT	GAG	TTC	ATC	CGG	GTC	TGG	GCT	GAA	TAC	GAC	5354
Gly	Pro	His	His	Leu	Asp	Glu	Phe	Ile	Arg	Val	Trp	Ala	Glu	Tyr	Asp	
			1725					1730					1735			
CCG	GCT	GCG	TGT	GGG	CGC	ATC	AGT	TAC	AAT	GAC	ATG	TTT	GAG	ATG	CTG	5402
Pro	Ala	Ala	Cys	Gly	Arg	Ile	Ser	Tyr	Asn	Asp	Met	Phe	Glu	Met	Leu	
		1740					1745					1750				
AAA	CAC	ATG	TCC	CCG	CCT	CTG	GGG	CTG	GGG	AAG	AAA	TGC	CCT	GCT	CGA	5450
Lys	His	Met	Ser	Pro	Pro	Leu	Gly	Leu	Gly	Lys	Lys	Cys	Pro	Ala	Arg	
		1755				1760					1765					
GTT	GCT	TAC	AAG	CGC	CTG	GTT	CGC	ATG	AAC	ATG	CCC	ATC	TCC	AAC	GAG	5498
Val	Ala	Tyr	Lys	Arg	Leu	Val	Arg	Met	Asn	Met	Pro	Ile	Ser	Asn	Glu	
1770					1775					1780					1785	
GAC	ATG	ACT	GTT	CAC	TTC	ACG	TCC	ACG	CTG	ATG	GCC	CTC	ATC	CGG	ACG	5546
Asp	Met	Thr	Val	His	Phe	Thr	Ser	Thr	Leu	Met	Ala	Leu	Ile	Arg	Thr	
				1790					1795					1800		
GCA	CTG	GAG	ATC	AAG	CTG	GCC	CCA	GCT	GGG	ACA	AAG	CAG	CAT	CAG	TGT	5594
Ala	Leu	Glu	Ile	Lys	Leu	Ala	Pro	Ala	Gly	Thr	Lys	Gln	His	Gln	Cys	
			1805				1810						1815			
GAC	GCG	GAG	TTG	AGG	AAG	GAG	ATT	TCC	GTT	GTG	TGG	GCC	AAT	CTG	CCC	5642
Asp	Ala	Glu	Leu	Arg	Lys	Glu	Ile	Ser	Val	Val	Trp	Ala	Asn	Leu	Pro	
		1820					1825					1830				

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CAG	AAG	ACT	TTG	GAC	TTG	CTG	GTA	CCA	CCC	CAT	AAG	CCT	GAT	GAG	ATG	5690
Gln	Lys	Thr	Leu	Asp	Leu	Leu	Val	Pro	Pro	His	Lys	Pro	Asp	Glu	Met	
	1835					1840					1845					
ACA	GTG	GGG	AAG	GTT	TAT	GCA	GCT	CTG	ATG	ATA	TTT	GAC	TTC	TAC	AAG	5738
Thr	Val	Gly	Lys	Val	Tyr	Ala	Ala	Leu	Met	Ile	Phe	Asp	Phe	Tyr	Lys	
1850					1855					1860					1865	
CAG	AAC	AAA	ACC	ACC	AGA	GAC	CAG	ATG	CAG	CAG	GCT	CCT	GGA	GGC	CTC	5786
Gln	Asn	Lys	Thr	Thr	Arg	Asp	Gln	Met	Gln	Gln	Ala	Pro	Gly	Gly	Leu	
				1870					1875					1880		
TCC	CAG	ATG	GGT	CCT	GTG	TCC	CTG	TTC	CAC	CCT	CTG	AAG	GCC	ACC	CTG	5834
Ser	Gln	Met	Gly	Pro	Val	Ser	Leu	Phe	His	Pro	Leu	Lys	Ala	Thr	Leu	
			1885					1890					1895			
GAG	CAG	ACA	CAG	CCG	GCT	GTG	CTC	CGA	GGA	GCC	CGG	GTT	TTC	CTT	CGA	5882
Glu	Gln	Thr	Gln	Pro	Ala	Val	Leu	Arg	Gly	Ala	Arg	Val	Phe	Leu	Arg	
	1900						1905					1910				
CAG	AAG	AGT	TCC	ACC	TCC	CTC	AGC	AAT	GGC	GGG	GCC	ATA	CAA	AAC	CAA	5930
Gln	Lys	Ser	Ser	Thr	Ser	Leu	Ser	Asn	Gly	Gly	Ala	Ile	Gln	Asn	Gln	
	1915					1920					1925					
GAG	AGT	GGC	ATC	AAA	GAG	TCT	GTC	TCC	TGG	GGC	ACT	CAA	AGG	ACC	CAG	5978
Glu	Ser	Gly	Ile	Lys	Glu	Ser	Val	Ser	Trp	Gly	Thr	Gln	Arg	Thr	Gln	
1930					1935					1940					1945	
GAT	GCA	CCC	CAT	GAG	GCC	AGG	CCA	CCC	CTG	GAG	CGT	GGC	CAC	TCC	ACA	6026
Asp	Ala	Pro	His	Glu	Ala	Arg	Pro	Pro	Leu	Glu	Arg	Gly	His	Ser	Thr	
				1950					1955					1960		
GAG	ATC	CCT	GTG	GGG	CGG	TCA	GGA	GCA	CTG	GCT	GTG	GAC	GTT	CAG	ATG	6074
Glu	Ile	Pro	Val	Gly	Arg	Ser	Gly	Ala	Leu	Ala	Val	Asp	Val	Gln	Met	
			1965					1970					1975			
CAG	AGC	ATA	ACC	CGG	AGG	GGC	CCT	GAT	GGG	GAG	CCC	CAG	CCT	GGG	CTG	6122
Gln	Ser	Ile	Thr	Arg	Arg	Gly	Pro	Asp	Gly	Glu	Pro	Gln	Pro	Gly	Leu	
		1980					1985					1990				
GAG	AGC	CAG	GGT	CGA	GCG	GCC	TCC	ATG	CCC	CGC	CTT	GCG	GCC	GAG	ACT	6170
Glu	Ser	Gln	Gly	Arg	Ala	Ala	Ser	Met	Pro	Arg	Leu	Ala	Ala	Glu	Thr	
	1995					2000					2005					
CAG	CCC	GTC	ACA	GAT	GCC	AGC	CCC	ATG	AAG	CGC	TCC	ATC	TCC	ACG	CTG	6218
Gln	Pro	Val	Thr	Asp	Ala	Ser	Pro	Met	Lys	Arg	Ser	Ile	Ser	Thr	Leu	
2010					2015					2020					2025	
GCC	CAG	CGG	CCC	CGT	GGG	ACT	CAT	CTT	TGC	AGC	ACC	ACC	CCG	GAC	CGC	6266
Ala	Gln	Arg	Pro	Arg	Gly	Thr	His	Leu	Cys	Ser	Thr	Thr	Pro	Asp	Arg	
				2030					2035					2040		
CCA	CCC	CCT	AGC	CAG	GCG	TCG	TCG	CAC	CAC	CAC	CAC	CAC	CGC	TGC	CAC	6314
Pro	Pro	Pro	Ser	Gln	Ala	Ser	Ser	His	His	His	His	His	Arg	Cys	His	
			2045					2050					2055			

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CGC CGC AGG GAC AGG AAG CAG AGG TCC CTG GAG AAG GGG CCC AGC CTG Arg Arg Arg Asp Arg Lys Gln Arg Ser Leu Glu Lys Gly Pro Ser Leu 2060 2065 2070	6362
TCT GCC GAT ATG GAT GGC GCA CCA AGC AGT GCT GTG GGG CCG GGG CTG Ser Ala Asp Met Asp Gly Ala Pro Ser Ser Ala Val Gly Pro Gly Leu 2075 2080 2085	6410
CCC CCG GGA GAG GGG CCT ACA GGC TGC CGG CGG GAA CGA GAG CGC CGG Pro Pro Gly Glu Gly Pro Thr Gly Cys Arg Arg Glu Arg Glu Arg Arg 2090 2095 2100 2105	6458
CAG GAG CGG GGC CGG TCC CAG GAG CGG AGG CAG CCC TCA TCC TCC TCC Gln Glu Arg Gly Arg Ser Gln Glu Arg Arg Gln Pro Ser Ser Ser Ser 2110 2115 2120	6506
TCG GAG AAG CAG CGC TTC TAC TCC TGC GAC CGC TTT GGG GGC CGT GAG Ser Glu Lys Gln Arg Phe Tyr Ser Cys Asp Arg Phe Gly Gly Arg Glu 2125 2130 2135	6554
CCC CCG AAG CCC AAG CCC TCC CTC AGC AGC CAC CCA ACG TCG CCA ACA Pro Pro Lys Pro Lys Pro Ser Leu Ser Ser His Pro Thr Ser Pro Thr 2140 2145 2150	6602
GCT GGC CAG GAG CCG GGA CCC CAC CCA CAG GCC GGC TCA GCC GTG GGC Ala Gly Gln Glu Pro Gly Pro His Pro Gln Ala Gly Ser Ala Val Gly 2155 2160 2165	6650
TTT CCG AAC ACA ACG CCC TGC TGC AGA GAG ACC CCC TCA GCC AGC CCC Phe Pro Asn Thr Thr Pro Cys Cys Arg Glu Thr Pro Ser Ala Ser Pro 2170 2175 2180 2185	6698
TGG CCC CTG GCT CTC GAA TTG GCT CTG ACC CTT ACC TGG GGC AGC GTC Trp Pro Leu Ala Leu Glu Leu Ala Leu Thr Leu Thr Trp Gly Ser Val 2190 2195 2200	6746
TGG ACA GTG AGG CCT CTG TCC ACG CCC TGC CTG AGG ACA CGC TCA CTT Trp Thr Val Arg Pro Leu Ser Thr Pro Cys Leu Arg Thr Arg Ser Leu 2205 2210 2215	6794
TCG AGG AGG CTG TGG CCA CCA ACT CGG GCC GCT CCT CCA GGA CTT CCT Ser Arg Arg Leu Trp Pro Pro Thr Arg Ala Ala Pro Pro Gly Leu Pro 2220 2225 2230	6842
ACG TGT CCT CCC TGACCTCCCA GTCTCACCCT CTCCGCCGCG TGCCCAACGG Thr Cys Pro Pro 2235	6894
TTACCACTGC ACCCTGGGAC TCAGCTCGGG TGGCCGAGCA CGGCACAGCT ACCACCACCC	6954
TGACCAAGAC CACTGGTGCT AGCTGCACCG TGACCGCTCA GACGCCTGCA TGCAGCAGGC	7014
GTGTGTTCCA GTGGATGAGT TTTATCATCC ACACGGGGCA GTCGGCCCTC GGGGGAGGCC	7074
TTGCCACCT TGGTGAGGCT CCTGTGGCCC CTCCCTCCCC CTCCTCCCT CTTTTACTCT	7134

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AGACGACGAA TAAAGCCCTG TTGCTTGAGT GTACGTACCG C

7175

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1546 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1437

(ix) FEATURE:

- (A) NAME/KEY: 3'UTR
- (B) LOCATION: 1435..1546

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

ATG GTC CAG AAG ACC AGC ATG TCC CGG GGC CCT TAC CCA CCC TCC CAG	48
Met Val Gln Lys Thr Ser Met Ser Arg Gly Pro Tyr Pro Pro Ser Gln	
1 5 10 15	
GAG ATC CCC ATG GAG GTC TTC GAC CCC AGC CCG CAG GGC AAA TAC AGC	96
Glu Ile Pro Met Glu Val Phe Asp Pro Ser Pro Gln Gly Lys Tyr Ser	
20 25 30	
AAG AGG AAA GGG CGA TTC AAA CGG TCA GAT GGG AGC ACG TCC TCG GAT	144
Lys Arg Lys Gly Arg Phe Lys Arg Ser Asp Gly Ser Thr Ser Ser Asp	
35 40 45	
ACC ACA TCC AAC AGC TTT GTC CGC CAG GGC TCA GCG GAG TCC TAC ACC	192
Thr Thr Ser Asn Ser Phe Val Arg Gln Gly Ser Ala Glu Ser Tyr Thr	
50 55 60	
AGC CGT CCA TCA GAC TCT GAT GTA TCT CTG GAG GAG GAC CGG GAA GCC	240
Ser Arg Pro Ser Asp Ser Asp Val Ser Leu Glu Glu Asp Arg Glu Ala	
65 70 75 80	
TTA AGG AAG GAA GCA GAG CGC CAG GCA TTA GCG CAG CTC GAG AAG GCC	288
Leu Arg Lys Glu Ala Glu Arg Gln Ala Leu Ala Gln Leu Glu Lys Ala	
85 90 95	
AAG ACC AAG CCA GTG GCA TTT GCT GTG CGG ACA AAT GTT GGC TAC AAT	336
Lys Thr Lys Pro Val Ala Phe Ala Val Arg Thr Asn Val Gly Tyr Asn	
100 105 110	
CCG TCT CCA GGG GAT GAG GTG CCT GTG CAG GGA GTG GCC ATC ACC TTC	384
Pro Ser Pro Gly Asp Glu Val Pro Val Gln Gly Val Ala Ile Thr Phe	
115 120 125	

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GAG	CCC	AAA	GAC	TTC	CTG	CAC	ATC	AAG	GAG	AAA	TAC	AAT	AAT	GAC	TGG	432
Glu	Pro	Lys	Asp	Phe	Leu	His	Ile	Lys	Glu	Lys	Tyr	Asn	Asn	Asp	Trp	
	130					135					140					
TGG	ATC	GGG	CGG	CTG	GTG	AAG	GAG	GGC	TGT	GAG	GTT	GGC	TTC	ATT	CCC	480
Trp	Ile	Gly	Arg	Leu	Val	Lys	Glu	Gly	Cys	Glu	Val	Gly	Phe	Ile	Pro	
145					150					155					160	
AGC	CCC	GTC	AAA	CTG	GAC	AGC	CTT	CGC	CTG	CTG	CAG	GAA	CAG	AAG	CTG	528
Ser	Pro	Val	Lys	Leu	Asp	Ser	Leu	Arg	Leu	Leu	Gln	Glu	Gln	Lys	Leu	
				165					170					175		
CGC	CAG	AAC	CGC	CTC	GGC	TCC	AGC	AAA	TCA	GGC	GAT	AAC	TCC	AGT	TCC	576
Arg	Gln	Asn	Arg	Leu	Gly	Ser	Ser	Lys	Ser	Gly	Asp	Asn	Ser	Ser	Ser	
			180					185					190			
AGT	CTG	GGA	GAT	GTG	GTG	ACT	GGC	ACC	CGC	CGC	CCC	ACA	CCC	CCT	GCC	624
Ser	Leu	Gly	Asp	Val	Val	Thr	Gly	Thr	Arg	Arg	Pro	Thr	Pro	Pro	Ala	
		195					200					205				
AGT	GCC	AAA	CAG	AAG	CAG	AAG	TCG	ACA	GAG	CAT	GTG	CCC	CCC	TAT	GAC	672
Ser	Ala	Lys	Gln	Lys	Gln	Lys	Ser	Thr	Glu	His	Val	Pro	Pro	Tyr	Asp	
	210					215					220					
GTG	GTG	CCT	TCC	ATG	AGG	CCC	ATC	ATC	CTG	GTG	GGA	CCG	TCG	CTC	AAG	720
Val	Val	Pro	Ser	Met	Arg	Pro	Ile	Ile	Leu	Val	Gly	Pro	Ser	Leu	Lys	
225					230					235					240	
GGC	TAC	GAG	GTT	ACA	GAC	ATG	ATG	CAG	AAA	GCT	TTA	TTT	GAC	TTC	TTG	768
Gly	Tyr	Glu	Val	Thr	Asp	Met	Met	Gln	Lys	Ala	Leu	Phe	Asp	Phe	Leu	
				245					250					255		
AAG	CAT	CGG	TTT	GAT	GGC	AGG	ATC	TCC	ATC	ACT	CGT	GTG	ACG	GCA	GAT	816
Lys	His	Arg	Phe	Asp	Gly	Arg	Ile	Ser	Ile	Thr	Arg	Val	Thr	Ala	Asp	
			260					265					270			
ATT	TCC	CTG	GCT	AAG	CGC	TCA	GTT	CTC	AAC	AAC	CCC	AGC	AAA	CAC	ATC	864
Ile	Ser	Leu	Ala	Lys	Arg	Ser	Val	Leu	Asn	Asn	Pro	Ser	Lys	His	Ile	
		275					280					285				
ATC	ATT	GAG	CGC	TCC	AAC	ACA	CGC	TCC	AGC	CTG	GCT	GAG	GTG	CAG	AGT	912
Ile	Ile	Glu	Arg	Ser	Asn	Thr	Arg	Ser	Ser	Leu	Ala	Glu	Val	Gln	Ser	
	290					295					300					
GAA	ATC	GAG	CGA	ATC	TTC	GAG	CTG	GCC	CGG	ACC	CTT	CAG	TTG	GTC	GCT	960
Glu	Ile	Glu	Arg	Ile	Phe	Glu	Leu	Ala	Arg	Thr	Leu	Gln	Leu	Val	Ala	
305					310					315					320	
CTG	GAT	GCT	GAC	ACC	ATC	AAT	CAC	CCA	GCC	CAG	CTG	TCC	AAG	ACC	TCG	1008
Leu	Asp	Ala	Asp	Thr	Ile	Asn	His	Pro	Ala	Gln	Leu	Ser	Lys	Thr	Ser	
				325					330					335		
CTG	GCC	CCC	ATC	ATT	GTT	TAC	ATC	AAG	ATC	ACC	TCT	CCC	AAG	GTA	CTT	1056
L u	Ala	Pro	Ile	Ile	Val	Tyr	Ile	Lys	Ile	Thr	Ser	Pro	Lys	Val	Leu	
			340					345					350			

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CAA AGG CTC ATC AAG TCC CGA GGA AAG TCT CAG TCC AAA CAC CTC AAT	1104
Gln Arg Leu Ile Lys Ser Arg Gly Lys Ser Gln Ser Lys His Leu Asn	
355 360 365	
GTC CAA ATA GCG GCC TCG GAA AAG CTG GCA CAG TGC CCC CCT GAA ATG	1152
Val Gln Ile Ala Ala Ser Glu Lys Leu Ala Gln Cys Pro Pro Glu Met	
370 375 380	
TTT GAC ATC ATC CTG GAT GAG AAC CAA TTG GAG GAT GCC TGC GAG CAT	1200
Phe Asp Ile Ile Leu Asp Glu Asn Gln Leu Glu Asp Ala Cys Glu His	
385 390 395 400	
CTG GCG GAG TAC TTG GAA GCC TAT TGG AAG GCC ACA CAC CCG CCC AGC	1248
Leu Ala Glu Tyr Leu Glu Ala Tyr Trp Lys Ala Thr His Pro Pro Ser	
405 410 415	
AGC ACG CCA CCC AAT CCG CTG CTG AAC CGC ACC ATG GCT ACC GCA GCC	1296
Ser Thr Pro Pro Asn Pro Leu Leu Asn Arg Thr Met Ala Thr Ala Ala	
420 425 430	
CTG GCT GCC AGC CCT GCC CCT GTC TCC AAC CTC CAG GTA CAG GTG CTC	1344
Leu Ala Ala Ser Pro Ala Pro Val Ser Asn Leu Gln Val Gln Val Leu	
435 440 445	
ACC TCG CTC AGG AGA AAC CTC GGC TTC TGG GGC GGG CTG GAG TCC TCA	1392
Thr Ser Leu Arg Arg Asn Leu Gly Phe Trp Gly Gly Leu Glu Ser Ser	
450 455 460	
CAG CGG GGC AGT GTG GTG CCC CAG GAG CAG GAA CAT GCC ATG TAGTGGGCGC	1444
Gln Arg Gly Ser Val Val Pro Gln Glu Gln His Ala Met	
465 470 475	
CCTGCCCCGTC TTCCCTCCTG CTCTGGGGTTC GGAAGTGGAG TGCAGGGAAC ATGGAGGAGG	1504
AAGGGAAGAG CTTTATTTTG TAAAAAATA AGATGAGCGG CA	1546

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1851 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1797
- (D) OTHER INFORMATION: /standard_name= "Beta1-3"

(ix) FEATURE:

- (A) NAME/KEY: 3'UTR
- (B) LOCATION: 1795..1851

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

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ATG	GTC	CAG	AAG	ACC	AGC	ATG	TCC	CGG	GGC	CCT	TAC	CCA	CCC	TCC	CAG	48
Met	Val	Gln	Lys	Thr	Ser	Met	Ser	Arg	Gly	Pro	Tyr	Pro	Pro	Ser	Gln	
1				5					10					15		
GAG	ATC	CCC	ATG	GGA	GTC	TTC	GAC	CCC	AGC	CCG	CAG	GGC	AAA	TAC	AGC	96
Glu	Ile	Pro	Met	Gly	Val	Phe	Asp	Pro	Ser	Pro	Gln	Gly	Lys	Tyr	Ser	
			20					25					30			
AAG	AGG	AAA	GGG	CGA	TTC	AAA	CGG	TCA	GAT	GGG	AGC	ACG	TCC	TCG	GAT	144
Lys	Arg	Lys	Gly	Arg	Phe	Lys	Arg	Ser	Asp	Gly	Ser	Thr	Ser	Ser	Asp	
		35					40					45				
ACC	ACA	TCC	AAC	AGC	TTT	GTC	CGC	CAG	GGC	TCA	GCG	GAG	TCC	TAC	ACC	192
Thr	Thr	Ser	Asn	Ser	Phe	Val	Arg	Gln	Gly	Ser	Ala	Glu	Ser	Tyr	Thr	
	50					55					60					
AGC	CGT	CCA	TCA	GAC	TCT	GAT	GTA	TCT	CTG	GAG	GAG	GAC	CGG	GAA	GCC	240
Ser	Arg	Pro	Ser	Asp	Ser	Asp	Val	Ser	Leu	Glu	Glu	Asp	Arg	Glu	Ala	
65					70					75					80	
TTA	AGG	AAG	GAA	GCA	GAG	CGC	CAG	GCA	TTA	GCG	CAG	CTC	GAG	AAG	GCC	288
Leu	Arg	Lys	Glu	Ala	Glu	Arg	Gln	Ala	Leu	Ala	Gln	Leu	Glu	Lys	Ala	
				85					90					95		
AAG	ACC	AAG	CCA	GTG	GCA	TTT	GCT	GTG	CGG	ACA	AAT	GTT	GGC	TAC	AAT	336
Lys	Thr	Lys	Pro	Val	Ala	Phe	Ala	Val	Arg	Thr	Asn	Val	Gly	Tyr	Asn	
			100					105					110			
CCG	TCT	CCA	GGG	GAT	GAG	GTG	CCT	GTG	CAG	GGA	GTG	GCC	ATC	ACC	TTC	384
Pro	Ser	Pro	Gly	Asp	Glu	Val	Pro	Val	Gln	Gly	Val	Ala	Ile	Thr	Phe	
		115					120					125				
GAG	CCC	AAA	GAC	TTC	CTG	CAC	ATC	AAG	GAG	AAA	TAC	AAT	AAT	GAC	TGG	432
Glu	Pro	Lys	Asp	Phe	Leu	His	Ile	Lys	Glu	Lys	Tyr	Asn	Asn	Asp	Trp	
	130					135					140					
TGG	ATC	GGG	CGG	CTG	GTG	AAG	GAG	GGC	TGT	GAG	GTT	GGC	TTC	ATT	CCC	480
Trp	Ile	Gly	Arg	Leu	Val	Lys	Glu	Gly	Cys	Glu	Val	Gly	Phe	Ile	Pro	
145					150					155					160	
AGC	CCC	GTC	AAA	CTG	GAC	AGC	CTT	CGC	CTG	CTG	CAG	GAA	CAG	AAG	CTG	528
Ser	Pro	Val	Lys	Leu	Asp	Ser	Leu	Arg	Leu	Leu	Gln	Glu	Gln	Lys	Leu	
				165					170					175		
CGC	CAG	AAC	CGC	CTC	GGC	TCC	AGC	AAA	TCA	GGC	GAT	AAC	TCC	AGT	TCC	576
Arg	Gln	Asn	Arg	Leu	Gly	Ser	Ser	Lys	Ser	Gly	Asp	Asn	Ser	Ser	Ser	
			180					185					190			
AGT	CTG	GGA	GAT	GTG	GTG	ACT	GGC	ACC	CGC	CGC	CCC	ACA	CCC	CCT	GCC	624
Ser	Leu	Gly	Asp	Val	Val	Thr	Gly	Thr	Arg	Arg	Pro	Thr	Pro	Pro	Ala	
		195					200					205				
AGT	GCC	AAA	CAG	AAG	CAG	AAG	TCG	ACA	GAG	CAT	GTG	CCC	CCC	TAT	GAC	672
Ser	Ala	Lys	Gln	Lys	Gln	Lys	Ser	Thr	Glu	His	Val	Pro	Pro	Tyr	Asp	
	210					215					220					

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GTG	GTG	CCT	TCC	ATG	AGG	CCC	ATC	ATC	CTG	GTG	GGA	CCG	TCG	CTC	AAG	720
Val	Val	Pro	Ser	Met	Arg	Pro	Ile	Ile	Leu	Val	Gly	Pro	Ser	Leu	Lys	
225					230					235					240	
GGC	TAC	GAG	GTT	ACA	GAC	ATG	ATG	CAG	AAA	GCT	TTA	TTT	GAC	TTC	TTG	768
Gly	Tyr	Glu	Val	Thr	Asp	Met	Met	Gln	Lys	Ala	Leu	Phe	Asp	Phe	Leu	
				245					250					255		
AAG	CAT	CGG	TTT	GAT	GGC	AGG	ATC	TCC	ATC	ACT	CGT	GTG	ACG	GCA	GAT	816
Lys	His	Arg	Phe	Asp	Gly	Arg	Ile	Ser	Ile	Thr	Arg	Val	Thr	Ala	Asp	
			260					265					270			
ATT	TCC	CTG	GCT	AAG	CGC	TCA	GTT	CTC	AAC	AAC	CCC	AGC	AAA	CAC	ATC	864
Ile	Ser	Leu	Ala	Lys	Arg	Ser	Val	Leu	Asn	Asn	Pro	Ser	Lys	His	Ile	
		275					280					285				
ATC	ATT	GAG	CGC	TCC	AAC	ACA	CGC	TCC	AGC	CTG	GCT	GAG	GTG	CAG	AGT	912
Ile	Ile	Glu	Arg	Ser	Asn	Thr	Arg	Ser	Ser	Leu	Ala	Glu	Val	Gln	Ser	
	290					295					300					
GAA	ATC	GAG	CGA	ATC	TTC	GAG	CTG	GCC	CGG	ACC	CTT	CAG	TTG	GTC	GCT	960
Glu	Ile	Glu	Arg	Ile	Phe	Glu	Leu	Ala	Arg	Thr	Leu	Gln	Leu	Val	Ala	
305					310					315					320	
CTG	GAT	GCT	GAC	ACC	ATC	AAT	CAC	CCA	GCC	CAG	CTG	TCC	AAG	ACC	TCG	1008
Leu	Asp	Ala	Asp		Ile	Asn	His	Pro	Ala	Gln	Leu	Ser	Lys	Thr	Ser	
				325					330					335		
CTG	GCC	CCC	ATC	ATT	GTT	TAC	ATC	AAG	ATC	ACC	TCT	CCC	AAG	GTA	CTT	1056
Leu	Ala	Pro	Ile	Ile	Val	Tyr	Ile	Lys	Ile	Thr	Ser	Pro	Lys	Val	Leu	
			340					345					350			
CAA	AGG	CTC	ATC	AAG	TCC	CGA	GGA	AAG	TCT	CAG	TCC	AAA	CAC	CTC	AAT	1104
Gln	Arg	Leu	Ile	Lys	Ser	Arg	Gly	Lys	Ser	Gln	Ser	Lys	His	Leu	Asn	
		355					360					365				
GTC	CAA	ATA	GCG	GCC	TCG	GAA	AAG	CTG	GCA	CAG	TGC	CCC	CCT	GAA	ATG	1152
Val	Gln	Ile	Ala	Ala	Ser	Glu	Lys	Leu	Ala	Gln	Cys	Pro	Pro	Glu	Met	
	370					375					380					
TTT	GAC	ATC	ATC	CTG	GAT	GAG	AAC	CAA	TTG	GAG	GAT	GCC	TGC	GAG	CAT	1200
Phe	Asp	Ile	Ile	Leu	Asp	Glu	Asn	Gln	Leu	Glu	Asp	Ala	Cys	Glu	His	
385					390					395					400	
CTG	GCG	GAG	TAC	TTG	GAA	GCC	TAT	TGG	AAG	GCC	ACA	CAC	CCG	CCC	AGC	1248
Leu	Ala	Glu	Tyr	Leu	Glu	Ala	Tyr	Trp	Lys	Ala	Thr	His	Pro	Pro	Ser	
				405					410					415		
AGC	ACG	CCA	CCC	AAT	CCG	CTG	CTG	AAC	CGC	ACC	ATG	GCT	ACC	GCA	GCC	1296
Ser	Thr	Pro	Pro	Asn	Pro	Leu	Leu	Asn	Arg	Thr	Met	Ala	Thr	Ala	Ala	
			420					425					430			
CTG	GCT	GCC	AGC	CCT	GCC	CCT	GTC	TCC	AAC	CTC	CAG	GGA	CCC	TAC	CTT	1344
Leu	Ala	Ala	Ser	Pro	Ala	Pro	Val	Ser	Asn	Leu	Gln	Gly	Pro	Tyr	Leu	
		435					440					445				

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GCT TCC GGG GAC CAG CCA CTG GAA CGG GCC ACC GGG GAG CAC GCC AGC	1392
Ala Ser Gly Asp Gln Pro Leu Glu Arg Ala Thr Gly Glu His Ala Ser	
450 455 460	
ATG CAC GAG TAC CCA GGG GAG CTG GGC CAG CCC CCA GGC CTT TAC CCC	1440
Met His Glu Tyr Pro Gly Glu Leu Gly Gln Pro Pro Gly Leu Tyr Pro	
465 470 475 480	
AGC AGC CAC CCA CCA GGC CGG GCA GGC ACG CTA CGG GCA CTG TCC CGC	1488
Ser Ser His Pro Pro Gly Arg Ala Gly Thr Leu Arg Ala Leu Ser Arg	
485 490 495	
CAA GAC ACT TTT GAT GCC GAC ACC CCC GGC AGC CGA AAC TCT GCC TAC	1536
Gln Asp Thr Phe Asp Ala Asp Thr Pro Gly Ser Arg Asn Ser Ala Tyr	
500 505 510	
ACG GAG CTG GGA GAC TCA TGT GTG GAC ATG GAG ACT GAC CCC TCA GAG	1584
Thr Glu Leu Gly Asp Ser Cys Val Asp Met Glu Thr Asp Pro Ser Glu	
515 520 525	
GGG CCA GGG CTT GGA GAC CCT GCA GGG GGC GGC ACG CCC CCA GCC CGA	1632
Gly Pro Gly Leu Gly Asp Pro Ala Gly Gly Gly Thr Pro Pro Ala Arg	
530 535 540	
CAG GGA TCC TGG GAG GAC GAG GAA GAA GAC TAT GAG GAA GAG CTG ACC	1680
Gln Gly Ser Trp Glu Asp Glu Glu Glu Asp Tyr Glu Glu Glu Leu Thr	
545 550 555 560	
GAC AAC CGG AAC CGG GGC CGG AAT AAG GCC CGC TAC TGC GCT GAG GGT	1728
Asp Asn Arg Asn Arg Gly Arg Asn Lys Ala Arg Tyr Cys Ala Glu Gly	
565 570 575	
GGG GGT CCA GTT TTG GGG CGC AAC AAG AAT GAG CTG GAG GGC TGG GGA	1776
Gly Gly Pro Val Leu Gly Arg Asn Lys Asn Glu Leu Glu Gly Trp Gly	
580 585 590	
CGA GGC GTC TAC ATT CGC TGAGAGGCAG GGGCCACACG GCGGGAGGAA	1824
Arg Gly Val Tyr Ile Arg	
595	
GGGCTCTGAG CCCAGGGGAG GGGAGGG	1851

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3600 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 35..3310
- (D) OTHER INFORMATION: /standard_name= "Alpha-2"

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(ix) FEATURE:

(A) NAME/KEY: 5'UTR

(B) LOCATION: 1..34

(ix) FEATURE:

(A) NAME/KEY: 3'UTR

(B) LOCATION: 3308..3600

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

CGCGGGGAGG GGGCATTGAT CTTGATCGC GAAG ATG GCT GCT GGC TGC CTG	52
Met Ala Ala Gly Cys Leu	
1 5	
CTG GCC TTG ACT CTG ACA CTT TTC CAA TCT TTG CTC ATC GGC CCC TCG	100
Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser Leu Leu Ile Gly Pro Ser	
10 15 20	
TCG GAG GAG CCG TTC CCT TCG GCC GTC ACT ATC AAA TCA TGG GTG GAT	148
Ser Glu Glu Pro Phe Pro Ser Ala Val Thr Ile Lys Ser Trp Val Asp	
25 30 35	
AAG ATG CAA GAA GAC CTT GTC ACA CTG GCA AAA ACA GCA AGT GGA GTC	196
Lys Met Gln Glu Asp Leu Val Thr Leu Ala Lys Thr Ala Ser Gly Val	
40 45 50	
AAT CAG CTT GTT GAT ATT TAT GAG AAA TAT CAA GAT TTG TAT ACT GTG	244
Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr Gln Asp Leu Tyr Thr Val	
55 60 65 70	
GAA CCA AAT AAT GCA CGC CAG CTG GTA GAA ATT GCA GCC AGG GAT ATT	292
Glu Pro Asn Asn Ala Arg Gln Leu Val Glu Ile Ala Ala Arg Asp Ile	
75 80 85	
GAG AAA CTT CTG AGC AAC AGA TCT AAA GCC CTG GTG AGC CTG GCA TTG	340
Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala Leu Val Ser Leu Ala Leu	
90 95 100	
GAA GCG GAG AAA GTT CAA GCA GCT CAC CAG TGG AGA GAA GAT TTT GCA	388
Glu Ala Glu Lys Val Gln Ala Ala His Gln Trp Arg Glu Asp Phe Ala	
105 110 115	
AGC AAT GAA GTT GTC TAC TAC AAT GCA AAG GAT GAT CTC GAT CCT GAG	436
Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys Asp Asp Leu Asp Pro Glu	
120 125 130	
AAA AAT GAC AGT GAG CCA GGC AGC CAG AGG ATA AAA CCT GTT TTC ATT	484
Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg Ile Lys Pro Val Phe Ile	
135 140 145 150	
GAA GAT GCT AAT TTT GGA CGA CAA ATA TCT TAT CAG CAC GCA GCA GTC	532
Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser Tyr Gln His Ala Ala Val	
155 160 165	
CAT ATT CCT ACT GAC ATC TAT GAG GGC TCA ACA ATT GTG TTA AAT GAA	580
His Ile Pro Thr Asp Ile Tyr Glu Gly Ser Thr Ile Val Leu Asn Glu	

395

400

405

BNSDOCID: <WO___9504822A1_I_>

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615	620	625	630	
AAG GAT TCG GAA ACC CTG AAG CCA GAT AAT TTT GAA GAA TCT GGC TAT				1972
Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn Phe Glu Glu Ser Gly Tyr	635	640	645	
ACA TTC ATA GCA CCA AGA GAT TAC TGC AAT GAC CTG AAA ATA TCG GAT				2020
Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn Asp Leu Lys Ile Ser Asp	650	655	660	
AAT AAC ACT GAA TTT CTT TTA AAT TTC AAC GAG TTT ATT GAT AGA AAA				2068
Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn Glu Phe Ile Asp Arg Lys	665	670	675	
ACT CCA AAC AAC CCA TCA TGT AAC GCG GAT TTG ATT AAT AGA GTC TTG				2116
Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp Leu Ile Asn Arg Val Leu	680	685	690	
CTT GAT GCA GGC TTT ACA AAT GAA CTT GTC CAA AAT TAC TGG AGT AAG				2164
Leu Asp Ala Gly Phe Thr Asn Glu Leu Val Gln Asn Tyr Trp Ser Lys	695	700	705	710
CAG AAA AAT ATC AAG GGA GTG AAA GCA CGA TTT GTT GTG ACT GAT GGT				2212
Gln Lys Asn Ile Lys Gly Val Lys Ala Arg Phe Val Val Thr Asp Gly	715	720	725	
GGG ATT ACC AGA GTT TAT CCC AAA GAG GCT GGA GAA AAT TGG CAA GAA				2260
Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala Gly Glu Asn Trp Gln Glu	730	735	740	
AAC CCA GAG ACA TAT GAG GAC AGC TTC TAT AAA AGG AGC CTA GAT AAT				2308
Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr Lys Arg Ser Leu Asp Asn	745	750	755	
GAT AAC TAT GTT TTC ACT GCT CCC TAC TTT AAC AAA AGT GGA CCT GGT				2356
Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe Asn Lys Ser Gly Pro Gly	760	765	770	
GCC TAT GAA TCG GGC ATT ATG GTA AGC AAA GCT GTA GAA ATA TAT ATT				2404
Ala Tyr Glu Ser Gly Ile Met Val Ser Lys Ala Val Glu Ile Tyr Ile	775	780	785	790
CAA GGG AAA CTT CTT AAA CCT GCA GTT GTT GGA ATT AAA ATT GAT GTA				2452
Gln Gly Lys Leu Leu Lys Pro Ala Val Val Gly Ile Lys Ile Asp Val	795	800	805	
AAT TCC TGG ATA GAG AAT TTC ACC AAA ACC TCA ATC AGA GAT CCG TGT				2500
Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr Ser Ile Arg Asp Pro Cys	810	815	820	
GCT GGT CCA GTT TGT GAC TGC AAA AGA AAC AGT GAC GTA ATG GAT TGT				2548
Ala Gly Pro Val Cys Asp Cys Lys Arg Asn Ser Asp Val Met Asp Cys	825	830	835	
GTG ATT CTG GAT GAT GGT GGG TTT CTT CTG ATG GCA AAT CAT GAT GAT				2596
Val Ile Leu Asp Asp Gly Gly Phe Leu Leu Met Ala Asn His Asp Asp				

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840	845	850	
TAT ACT AAT CAG ATT GGA AGA TTT TTT GGA GAG ATT GAT CCC AGC TTG			2644
Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly Glu Ile Asp Pro Ser Leu			
855	860	865	870
ATG AGA CAC CTG GTT AAT ATA TCA GTT TAT GCT TTT AAC AAA TCT TAT			2692
Met Arg His Leu Val Asn Ile Ser Val Tyr Ala Phe Asn Lys Ser Tyr			
	875	880	885
GAT TAT CAG TCA GTA TGT GAG CCC GGT GCT GCA CCA AAA CAA GGA GCA			2740
Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala Ala Pro Lys Gln Gly Ala			
	890	895	900
GGA CAT CGC TCA GCA TAT GTG CCA TCA GTA GCA GAC ATA TTA CAA ATT			2788
Gly His Arg Ser Ala Tyr Val Pro Ser Val Ala Asp Ile Leu Gln Ile			
	905	910	915
GGC TGG TGG GCC ACT GCT GCT GCC TGG TCT ATT CTA CAG CAG TTT CTC			2836
Gly Trp Trp Ala Thr Ala Ala Trp Ser Ile Leu Gln Gln Phe Leu			
	920	925	930
TTG AGT TTG ACC TTT CCA CGA CTC CTT GAG GCA GTT GAG ATG GAG GAT			2884
Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu Ala Val Glu Met Glu Asp			
	935	940	945
GAT GAC TTC ACG GCC TCC CTG TCC AAG CAG AGC TGC ATT ACT GAA CAA			2932
Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln Ser Cys Ile Thr Glu Gln			
	955	960	965
ACC CAG TAT TTC TTC GAT AAC GAC AGT AAA TCA TTC AGT GGT GTA TTA			2980
Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys Ser Phe Ser Gly Val Leu			
	970	975	980
GAC TGT GGA AAC TGT TCC AGA ATC TTT CAT GGA GAA AAG CTT ATG AAC			3028
Asp Cys Gly Asn Cys Ser Arg Ile Phe His Gly Glu Lys Leu Met Asn			
	985	990	995
ACC AAC TTA ATA TTC ATA ATG GTT GAG AGC AAA GGG ACA TGT CCA TGT			3076
Thr Asn Leu Ile Phe Ile Met Val Glu Ser Lys Gly Thr Cys Pro Cys			
	1000	1005	1010
GAC ACA CGA CTG CTC ATA CAA GCG GAG CAG ACT TCT GAC GGT CCA AAT			3124
Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln Thr Ser Asp Gly Pro Asn			
	1015	1020	1025
CCT TGT GAC ATG GTT AAG CAA CCT AGA TAC CGA AAA GGG CCT GAT GTC			3172
Pro Cys Asp Met Val Lys Gln Pro Arg Tyr Arg Lys Gly Pro Asp Val			
	1035	1040	1045
TGC TTT GAT AAC AAT GTC TTG GAG GAT TAT ACT GAC TGT GGT GGT GTT			3220
Cys Phe Asp Asn Asn Val Leu Glu Asp Tyr Thr Asp Cys Gly Gly Val			
	1050	1055	1060
TCT GGA TTA AAT CCC TCC CTG TGG TAT ATC ATT GGA ATC CAG TTT CTA			3268
Ser Gly Leu Asn Pro Ser Leu Trp Tyr Ile Ile Gly Ile Gln Phe Leu			

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1065	1070	1075	
CTA CTT TGG CTG GTA TCT GGC AGC ACA CAC CGG	CTG TTA TGACCTTCTA	3317	
Leu Leu Trp Leu Val Ser Gly Ser Thr His Arg	Leu Leu		
1080	1085 1090		
AAAACCAAAT CTGCATAGTT AAACCTCCAGA CCCTGCCAAA	ACATGAGCCC TGCCCTCAAT	3377	
TACAGTAACG TAGGGTCAGC TATAAAATCA GACAAACATT	AGCTGGGCCT GTTCCATGGC	3437	
ATAACACTAA GGCAGACT CCTAAGGCAC CCACTGGCTG	CATGTCAGGG TGTCAGATCC	3497	
TTAAACGTGT GTGAATGCTG CATCATCTAT GTGTAACATC	AAAGCAAAAT CCTATACGTG	3557	
TCCTCTATTG GAAAATTTGG GCGTTTGTG TTGCATTGTT	GGT	3600	

(2) INFORMATION FOR SEQ ID NO:12:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 323 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CCCCCTGCCA GTGGCCAAAC AGAAGCAGAA GTCGGGTAAT GAAATGACTA ACTTAGCCTT	60
TGAAGTAGAC CCCCTAGAGT TAGAGGAGGA AGAGGCTGAG CTTGGTGAGC AGAGTGGCTC	120
TGCCAAGACT AGTGTTAGCA GTGTCACCAC CCCGCCACCC CATGGCAAAC GCATCCCCCTT	180
CTTTAAGAAG ACAGAGCATG TGCCCCCCTA TGACGTGGTG CTTTCCATGA GGCCCATCAT	240
CCTGGTGGGA CCGTCGCTCA AGGGCTACGA GGTTACAGAC ATGATGCAGA AAGCTTTATT	300
TGACTTCTTG AAGCATCGGT TTG	323

(2) INFORMATION FOR SEQ ID NO:13:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 57 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CCTATTGGTG TAGGTATACC AACAATTAAT TTAAGAAAAA GGAGACCCAA TATCCAG	57
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(2) INFORMATION FOR SEQ ID NO:14:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 180 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (ix) FEATURE:
 - (A) NAME/KEY: CDS
 - (B) LOCATION: 1..132

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

TGG TCC TTT GCC TGC GCC TGT GCC GCC TTC ATC CTC CTC TTT CTC GGC	48
Trp Ser Phe Ala Cys Ala Cys Ala Ala Phe Ile Leu Leu Phe Leu Gly	
1 5 10 15	
GGT CTC GCC CTC CTG CTG TTC TCC CTG CCT CGA ATG CCC CGG AAC CCA	96
Gly Leu Ala Leu Leu Leu Phe Ser Leu Pro Arg Met Pro Arg Asn Pro	
20 25 30	
TGG GAG TCC TGC ATG GAT GCT GAG CCC GAG CAC TAACCCTCCT GCGGCCCTAG	149
Trp Glu Ser Cys Met Asp Ala Glu Pro Glu His	
35 40	
CGACCCTCAG GCTTCTTCCC AGGAAGCGGG G	180

(2) INFORMATION FOR SEQ ID NO:15:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 22 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: Other nucleic acid;
 - (A) DESCRIPTION: Oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

AATTCGGTAC GTACACTCGA GC	22
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(2) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: Other nucleic acid;
 - (A) DESCRIPTION: Oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

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GCTCGAGTGT ACGTACCG

18

(2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: Other nucleic acid;
 - (A) DESCRIPTION: Oligonucleotide

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CCATGGTACC TTCGTTGACG

20

(2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 24 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: Other nucleic acid;
 - (A) DESCRIPTION: Oligonucleotide

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

AATTCGTCAA CGAAGGTACC ATGG

24

(2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2153 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 53..1504
- (D) OTHER INFORMATION: /standard_name= "Beta-3-1"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

CCGCCTCGGA CCCCCTGTCC CGGGGGAGGG GGAGAGCCCG CTACCCTGGT CT ATG
Met
1

55

TCT TTT TCT GAC TCC AGT GCA ACC TTC CTG CTG AAC GAG GGT TCA GCC

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Ser	Phe	Ser	Asp 5	Ser	Ser	Ala	Thr	Phe 10	Leu	Leu	Asn	Glu	Gly 15	Ser	Ala		
GAC	TCC	TAC	ACC	AGC	CGC	CCA	TCT	CTG	GAC	TCA	GAC	GTC	TCC	CTG	GAG	151	
Asp	Ser	Tyr 20	Thr	Ser	Arg	Pro	Ser 25	Leu	Asp	Ser	Asp	Val 30	Ser	Leu	Glu		
GAG	GAC	CGG	GAG	AGT	GCC	CGG	CGT	GAA	GTA	GAG	AGC	CAG	GCT	CAG	CAG	199	
Glu	Asp 35	Arg	Glu	Ser	Ala	Arg 40	Arg	Glu	Val	Glu	Ser 45	Gln	Ala	Gln	Gln		
CAG	CTC	GAA	AGG	GCC	AAG	CAC	AAA	CCT	GTG	GCA	TTT	GCG	GTG	AGG	ACC	247	
Gln	Leu	Glu	Arg	Ala	Lys 55	His	Lys	Pro	Val	Ala 60	Phe	Ala	Val	Arg	Thr 65		
AAT	GTC	AGC	TAC	TGT	GGC	GTA	CTG	GAT	GAG	GAG	TGC	CCA	GTC	CAG	GGC	295	
Asn	Val	Ser	Tyr	Cys 70	Gly	Val	Leu	Asp	Glu 75	Glu	Cys	Pro	Val	Gln	Gly 80		
TCT	GGA	GTC	AAC	TTT	GAG	GCC	AAA	GAT	TTT	CTG	CAC	ATT	AAA	GAG	AAG	343	
Ser	Gly	Val	Asn 85	Phe	Glu	Ala	Lys	Asp 90	Phe	Leu	His	Ile	Lys 95	Glu	Lys		
TAC	AGC	AAT	GAC	TGG	TGG	ATC	GGG	CGG	CTA	GTG	AAA	GAG	GGC	GGG	GAC	391	
Tyr	Ser	Asn 100	Asp	Trp	Trp	Ile	Gly 105	Arg	Leu	Val	Lys	Glu 110	Gly	Gly	Asp		
ATC	GCC	TTC	ATC	CCC	AGC	CCC	CAG	CGC	CTG	GAG	AGC	ATC	CGG	CTC	AAA	439	
Ile	Ala	Phe	Ile	Pro	Ser	Pro 120	Gln	Arg	Leu	Glu	Ser 125	Ile	Arg	Leu	Lys		
CAG	GAG	CAG	AAG	GCC	AGG	AGA	TCT	GGG	AAC	CCT	TCC	AGC	CTG	AGT	GAC	487	
Gln	Glu	Gln	Lys	Ala	Arg 135	Arg	Ser	Gly	Asn	Pro 140	Ser	Ser	Leu	Ser	Asp 145		
ATT	GGC	AAC	CGA	CGC	TCC	CCT	CCG	CCA	TCT	CTA	GCC	AAG	CAG	AAG	CAA	535	
Ile	Gly	Asn	Arg	Arg 150	Ser	Pro	Pro	Pro	Ser 155	Leu	Ala	Lys	Gln	Lys 160	Gln		
AAG	CAG	GCG	GAA	CAT	GTT	CCC	CCG	TAT	GAC	GTG	GTG	CCC	TCC	ATG	CGG	583	
Lys	Gln	Ala	Glu 165	His	Val	Pro	Pro	Tyr 170	Asp	Val	Val	Pro	Ser 175	Met	Arg		
CCT	GTG	GTG	CTG	GTG	GGA	CCC	TCT	CTG	AAA	GGT	TAT	GAG	GTC	ACA	GAC	631	
Pro	Val	Val	Leu 180	Val	Gly	Pro	Ser 185	Leu	Lys	Gly	Tyr	Glu 190	Val	Thr	Asp		
ATG	ATG	CAG	AAG	GCT	CTC	TTC	GAC	TTC	CTC	AAA	CAC	AGA	TTT	GAT	GGC	679	
Met	Met	Gln	Lys	Ala	Leu	Phe 200	Asp	Phe	Leu	Lys	His 205	Arg	Phe	Asp	Gly		
AGG	ATC	TCC	ATC	ACC	CGA	GTC	ACA	GCC	GAC	CTC	TCC	CTG	GCA	AAG	CGA	727	
Arg	Ile	Ser	Ile	Thr	Arg 215	Val	Thr	Ala	Asp	Leu 220	Ser	Leu	Ala	Lys	Arg 225		
TCT	GTG	CTC	AAC	AAT	CCG	GGC	AAG	AGG	ACC	ATC	ATT	GAG	CGC	TCC	TCT	775	

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Ser	Val	Leu	Asn	Asn	Pro	Gly	Lys	Arg	Thr	Ile	Ile	Glu	Arg	Ser	Ser	
			230						235					240		
GCC	CGC	TCC	AGC	ATT	GCG	GAA	GTG	CAG	AGT	GAG	ATC	GAG	CGC	ATA	TTT	823
Ala	Arg	Ser	Ser	Ile	Ala	Glu	Val	Gln	Ser	Glu	Ile	Glu	Arg	Ile	Phe	
			245					250					255			
GAG	CTG	GCC	AAA	TCC	CTG	CAG	CTA	GTA	GTG	TTG	GAC	GCT	GAC	ACC	ATC	871
Glu	Leu	Ala	Lys	Ser	Leu	Gln	Leu	Val	Val	Leu	Asp	Ala	Asp	Thr	Ile	
		260					265					270				
AAC	CAC	CCA	GCA	CAG	CTG	GCC	AAG	ACC	TCG	CTG	GCC	CCC	ATC	ATC	GTC	919
Asn	His	Pro	Ala	Gln	Leu	Ala	Lys	Thr	Ser	Leu	Ala	Pro	Ile	Ile	Val	
	275					280					285					
TTT	GTC	AAA	GTG	TCC	TCA	CCA	AAG	GTA	CTC	CAG	CGT	CTC	ATT	CGC	TCC	967
Phe	Val	Lys	Val	Ser	Ser	Pro	Lys	Val	Leu	Gln	Arg	Leu	Ile	Arg	Ser	
290					295					300					305	
CGG	GGG	AAG	TCA	CAG	ATG	AAG	CAC	CTG	ACC	GTA	CAG	ATG	ATG	GCA	TAT	1015
Arg	Gly	Lys	Ser	Gln	Met	Lys	His	Leu	Thr	Val	Gln	Met	Met	Ala	Tyr	
				310					315					320		
GAT	AAG	CTG	GTT	CAG	TGC	CCA	CCG	GAG	TCA	TTT	GAT	GTG	ATT	CTG	GAT	1063
Asp	Lys	Leu	Val	Gln	Cys	Pro	Pro	Glu	Ser	Phe	Asp	Val	Ile	Leu	Asp	
			325					330					335			
GAG	AAC	CAG	CTG	GAG	GAT	GCC	TGT	GAG	CAC	CTG	GCT	GAG	TAC	CTG	GAG	1111
Glu	Asn	Gln	Leu	Glu	Asp	Ala	Cys	Glu	His	Leu	Ala	Glu	Tyr	Leu	Glu	
		340					345					350				
GTT	TAC	TGG	CGG	GCC	ACG	CAC	CAC	CCA	GCC	CCT	GGC	CCC	GGA	CTT	CTG	1159
Val	Tyr	Trp	Arg	Ala	Thr	His	His	Pro	Ala	Pro	Gly	Pro	Gly	Leu	Leu	
	355					360					365					
GGT	CCT	CCC	AGT	GCC	ATC	CCC	GGA	CTT	CAG	AAC	CAG	CAG	CTG	CTG	GGG	1207
Gly	Pro	Pro	Ser	Ala	Ile	Pro	Gly	Leu	Gln	Asn	Gln	Gln	Leu	Leu	Gly	
370					375					380					385	
GAG	CGT	GGC	GAG	GAG	CAC	TCC	CCC	CTT	GAG	CGG	GAC	AGC	TTG	ATG	CCC	1255
Glu	Arg	Gly	Glu	Glu	His	Ser	Pro	Leu	Glu	Arg	Asp	Ser	Leu	Met	Pro	
				390					395					400		
TCT	GAT	GAG	GCC	AGC	GAG	AGC	TCC	CGC	CAA	GCC	TGG	ACA	GGA	TCT	TCA	1303
Ser	Asp	Glu	Ala	Ser	Glu	Ser	Ser	Arg	Gln	Ala	Trp	Thr	Gly	Ser	Ser	
			405					410					415			
CAG	CGT	AGC	TCC	CGC	CAC	CTG	GAG	GAG	GAC	TAT	GCA	GAT	GCC	TAC	CAG	1351
Gln	Arg	Ser	Ser	Arg	His	Leu	Glu	Glu	Asp	Tyr	Ala	Asp	Ala	Tyr	Gln	
			420				425					430				
GAC	CTG	TAC	CAG	CCT	CAC	CGC	CAA	CAC	ACC	TCG	GGG	CTG	CCT	AGT	GCT	1399
Asp	Leu	Tyr	Gln	Pro	His	Arg	Gln	His	Thr	Ser	Gly	Leu	Pro	Ser	Ala	
	435					440					445					
AAC	GGG	CAT	GAC	CCC	CAA	GAC	CGG	CTT	CTA	GCC	CAG	GAC	TCA	GAA	CAC	1447

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Asn Gly His Asp Pro Gln Asp Arg Leu Leu Ala Gln Asp Ser Glu His
 450 455 460 465
 AAC CAC AGT GAC CGG AAC TGG CAG CGC AAC CGG CCT TGG CCC AAG GAT 1495
 Asn His Ser Asp Arg Asn Trp Gln Arg Asn Arg Pro Trp Pro Lys Asp
 470 475 480
 AGC TAC TGA CAG C CTCCTGCTGC CCTACCCTGG CAGGCACAGG 1543
 Ser Tyr *
 CGCAGCTGGC TGGGGGGCCC ACTCCAGGCA GGGTGGCGTT AGACTGGCAT 1593
 CAGGCTGGCA CTAGGCTCAG CCCCCAAAC CCCCTGCCCA GCCCCAGCTT CAGGGCTGCC 1648
 TGTGGTCCCA AGGTTCTGGG AGAAACAGGG GACCCCCTCA CCTCCTGGGC AGTGACCCCT 1708
 ACTAGGCTCC CATTCCAGGT ACTAGCTGTG TGTTCCTGCAC CCCTGGCACC TTCCTCTCCT 1768
 CCCACACAGG AAGCTGCCCC ACTGGGCAGT GCCCTCAGGC CAGGATCCCC TTAGCAGGGT 1828
 CCTTCCCACC AGACTCAGGG AAGGGATGCC CCATTAAAGT GACAAAAGGG TGGGTGTGGG 1888
 CACCATGGCA TGAGGAAGAA ACAAGGTCCC TGAGCAGGCA CAAGTCCTGA CAGTCAAGGG 1948
 ACTGCTTTGG CATCCAGGGC CTCCAGTCAC CTCACTGCCA TACATTAGAA ATGAGACAAT 2008
 TCAAAGCCCC CCCAGGGTGG CACACCCATC TGTGTGCTGGG GTGTGGCAGC CACATCCAAG 2068
 ACTGGAGCAG CAGGCTGGCC ACGCTTGGGC CAGAGAGAGC TCACAGCTGA AGCTCTTGGA 2128
 GGAAGGGCT CTCCTCACCC AATCG 2153

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2144 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 51..1492
- (D) OTHER INFORMATION: /product= "A Beta3 subunit of human calcium channel"

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

CGCCCCGGC GCCGCTCGTT CCCCCGACCC GGACTCCCCC ATGTATGACG ACTCCTACGT 60
 GCGCGGTTT GAGGACTCGG AGGCGGTTTC AGCCGACTCC TACACCAGCC GCCCATCTCT 120

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GGACTCAGAC GTCTCCCTGG AGGAGGACCG GGAGAGTGCC CGGCGTGAAG TAGAGAGCCA	180
GGCTCAGCAG CAGCTCGAAA GGGCCAAGCA CAAACCTGTG GCATTTGCGG TGAGGACCAA	240
TGTCAGCTAC TGTGGCGTAC TGGATGAGGA GTGCCCAGTC CAGGGCTCTG GAGTCAACTT	300
TGAGGCCAAA GATTTTCTGC ACATTAAAGA GAAGTACAGC AATGACTGGT GGATCGGGCG	360
GCTAGTGAAA GAGGGCGGGG ACATCGCCTT CATCCCCAGC CCCCAGCGCC TGGAGAGCAT	420
CCGGCTCAAA CAGGAGCAGA AGGCCAGGAG ATCTGGGAAC CCTTCAGCC TGAGTGACAT	480
TGGCAACCGA CGCTCCCCTC CGCCATCTCT AGCCAAGCAG AAGCAAAAGC AGGCGGAACA	540
TGTTCCCCCG TATGACGTGG TGCCCTCCAT GCGGCCTGTG GTGCTGGTGG GACCCTCTCT	600
GAAAGGTTAT GAGGTCACAG ACATGATGCA GAAGGCTCTC TTCGACTTCC TCAAACACAG	660
ATTTGATGGC AGGATCTCCA TCACCCGAGT CACAGCCGAC CTCTCCCTGG CAAAGCGATC	720
TGTGCTCAAC AATCCGGGCA AGAGGACCAT CATTGAGCGC TCCTCTGCCC GCTCCAGCAT	780
TGCGGAAGTG CAGAGTGAGA TCGAGCGCAT ATTTGAGCTG GCCAAATCCC TGCAGCTAGT	840
AGTGTGGAC GCTGACACCA TCAACCACCC AGCACAGCTG GCCAAGACCT CGCTGGCCCC	900
CATCATCGTC TTTGTCAAAG TGTCTCACC AAAGGTAATC CAGCGTCTCA TTCGCTCCCG	960
GGGGAAGTCA CAGATGAAGC ACCTGACCGT ACAGATGATG GCATATGATA AGCTGGTTCA	1020
GTGCCCACCG GAGTCATTTG ATGTGATTCT GGATGAGAAC CAGCTGGAGG ATGCCTGTGA	1080
GCACCTGGCT GAGTACCTGG AGGTTTACTG GCGGGCCACG CACCACCCAG CCCCTGGCCC	1140
CGGACTTCTG GGTCTCCCA GTGCCATCCC CGGACTTCAG AACCAGCAGC TGCTGGGGGA	1200
GCGTGCGAG GAGCACTCCC CCCTTGAGCG GGACAGCTTG ATGCCCTCTG ATGAGGCCAG	1260
CGAGAGCTCC CGCCAAGCCT GGACAGGATC TTCACAGCGT AGCTCCCGCC ACCTGGAGGA	1320
GGACTATGCA GATGCCTACC AGGACCTGTA CCAGCCTCAC CGCCAACACA CCTCGGGGCT	1380
GCCTAGTGCT AACGGGCATG ACCCCCAAGA CCGGCTTCTA GCCCAGGACT CAGAACACAA	1440
CCACAGTGAC CGGAACTGGC AGCGCAACCG GCCTTGGCCC AAGGATAGCT ACTGACAGCC	1500
TCCTGCTGCC CTACCCTGGC AGGCACAGGC GCAGCTGGCT GGGGGGCCCA CTCCAGGCAG	1560
GGTGGCGTTA GACTGGCATC AGGCTGGCAC TAGGCTCAGC CCCC AAAACC CCCTGCCAG	1620
CCCCAGCTTC AGGGCTGCCT GTGGTCCCAA GGTTCTGGGA GAAACAGGGG ACCCCCTCAC	1680
CTCCTGGGCA GTGACCCCTA CTAGGCTCCC ATTCCAGGTA CTAGCTGTGT GTTCTGCACC	1740
CCTGGCACCT TCCTCTCCTC CCACACAGGA AGCTGCCCCA CTGGGCAGTG CCCTCAGGCC	1800

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AGGATCCCCT TAGCAGGGTC CTTCCCACCA GACTCAGGGA AGGGATGCCC CATTAAAGTG      1860
ACAAAAGGGT GGGTGTGGGC ACCATGGCAT GAGGAAGAAA CAAGGTCCCT GAGCAGGCAC      1920
AAGTCCTGAC AGTCAAGGGA CTGCTTTGGC ATCCAGGGCC TCCAGTCACC TCACTGCCAT      1980
ACATTAGAAA TGAGACAATT CAAAGCCCCC CCAGGGTGGC ACACCCATCT GTTGCTGGGG      2040
TGTGGCAGCC ACATCCAAGA CTGGAGCAGC AGGCTGGCCA CGCTTGGGCC AGAGAGAGCT      2100
CACAGCTGAA GCTCTTGGAG GGAAGGGCTC TCCTCACCCA ATCG                        2144

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(2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 28 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: Other nucleic acid;
 - (A) DESCRIPTION: Oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

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CTCAGTACCA TCTCTGATAC CAGCCCCA                                     28

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(2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 7808 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 237..7769
- (D) OTHER INFORMATION: /standard_name= "Alpha-1A-1"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

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GATGTCCCGA GCTGCTATCC CCGGCTCGGC CCGGGCAGCC GCCTTCTGAG CCCCCGACCC      60
GAGGCGCCGA GCCGCCGCCG CCCGATGGGC TGGGCCGTGG AGCGTCTCCG CAGTCGTAGC      120
TCCAGCCGCC GCGCTCCCAG CCCCAGCAGC CTCAGCATCA GCGGCGGCGG CGGCGGCGGC      180
GGCGTCTTCC GCATCGTTCC CCGCAGCGTA ACCCGGAGCC CTTTGCTCTT TGCAGA        236
ATG GCC CGC TTC GGA GAC GAG ATG CCG GCC CGC TAC GGG GGA GGA GGC        284

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Met 1	Ala	Arg	Phe	Gly 5	Asp	Glu	Met	Pro	Ala 10	Arg	Tyr	Gly	Gly	Gly 15	Gly		
TCC	GGG	GCA	GCC	GCC	GGG	GTG	GTC	GTG	GGC	AGC	GGA	GGC	GGG	CGA	GGA		332
Ser	Gly	Ala	Ala	Ala	Gly	Val	Val	Val	Gly	Ser	Gly	Gly	Gly	Arg	Gly		
				20				25					30				
GCC	GGG	GGC	AGC	CGG	CAG	GGC	GGG	CAG	CCC	GGG	GCG	CAA	AGG	ATG	TAC		380
Ala	Gly	Gly	Ser	Arg	Gln	Gly	Gly	Gln	Pro	Gly	Ala	Gln	Arg	Met	Tyr		
			35				40					45					
AAG	CAG	TCA	ATG	GCG	CAG	AGA	GCG	CGG	ACC	ATG	GCA	CTC	TAC	AAC	CCC		428
Lys	Gln	Ser	Met	Ala	Gln	Arg	Ala	Arg	Thr	Met	Ala	Leu	Tyr	Asn	Pro		
	50					55					60						
ATC	CCC	GTC	CGA	CAG	AAC	TGC	CTC	ACG	GTT	AAC	CGG	TCT	CTC	TTC	CTC		476
Ile	Pro	Val	Arg	Gln	Asn	Cys	Leu	Thr	Val	Asn	Arg	Ser	Leu	Phe	Leu		
	65				70					75					80		
TTC	AGC	GAA	GAC	AAC	GTG	GTG	AGA	AAA	TAC	GCC	AAA	AAG	ATC	ACC	GAA		524
Phe	Ser	Glu	Asp	Asn	Val	Val	Arg	Lys	Tyr	Ala	Lys	Lys	Ile	Thr	Glu		
				85					90					95			
TGG	CCT	CCC	TTT	GAA	TAT	ATG	ATT	TTA	GCC	ACC	ATC	ATA	GCG	AAT	TGC		572
Trp	Pro	Pro	Phe	Glu	Tyr	Met	Ile	Leu	Ala	Thr	Ile	Ile	Ala	Asn	Cys		
			100					105					110				
ATC	GTC	CTC	GCA	CTG	GAG	CAG	CAT	CTG	CCT	GAT	GAT	GAC	AAG	ACC	CCG		620
Ile	Val	Leu	Ala	Leu	Glu	Gln	His	Leu	Pro	Asp	Asp	Asp	Lys	Thr	Pro		
		115					120					125					
ATG	TCT	GAA	CGG	CTG	GAT	GAC	ACA	GAA	CCA	TAC	TTC	ATT	GGA	ATT	TTT		668
Met	Ser	Glu	Arg	Leu	Asp	Asp	Thr	Glu	Pro	Tyr	Phe	Ile	Gly	Ile	Phe		
	130				135						140						
TGT	TTC	GAG	GCT	GGA	ATT	AAA	ATC	ATT	GCC	CTT	GGG	TTT	GCC	TTC	CAC		716
Cys	Phe	Glu	Ala	Gly	Ile	Lys	Ile	Ile	Ala	Leu	Gly	Phe	Ala	Phe	His		
	145				150					155					160		
AAA	GGC	TCC	TAC	TTG	AGG	AAT	GGC	TGG	AAT	GTC	ATG	GAC	TTT	GTG	GTG		764
Lys	Gly	Ser	Tyr	Leu	Arg	Asn	Gly	Trp	Asn	Val	Met	Asp	Phe	Val	Val		
				165				170						175			
GTG	CTA	ACG	GGC	ATC	TTG	GCG	ACA	GTT	GGG	ACG	GAG	TTT	GAC	CTA	CGG		812
Val	Leu	Thr	Gly	Ile	Leu	Ala	Thr	Val	Gly	Thr	Glu	Phe	Asp	Leu	Arg		
			180					185					190				
ACG	CTG	AGG	GCA	GTT	CGA	GTG	CTG	CGG	CCG	CTC	AAG	CTG	GTG	TCT	GGA		860
Thr	Leu	Arg	Ala	Val	Arg	Val	Leu	Arg	Pro	Leu	Lys	Leu	Val	Ser	Gly		
		195					200					205					
ATC	CCA	AGT	TTA	CAA	GTC	GTC	CTG	AAG	TCG	ATC	ATG	AAG	GCG	ATG	ATC		908
Ile	Pro	Ser	Leu	Gln	Val	Val	Leu	Lys	Ser	Ile	Met	Lys	Ala	Met	Ile		
	210					215					220						
CCT	TTG	CTG	CAG	ATC	GGC	CTC	CTC	CTA	TTT	TTT	GCA	ATC	CTT	ATT	TTT		956

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Pro 225	Leu	Leu	Gln	Ile	Gly 230	Leu	Leu	Leu	Phe	Phe 235	Ala	Ile	Leu	Ile	Phe 240	
GCA	ATC	ATA	GGG	TTA	GAA	TTT	TAT	ATG	GGA	AAA	TTT	CAT	ACC	ACC	TGC	1004
Ala	Ile	Ile	Gly	Leu	Glu	Phe	Tyr	Met	Gly 250	Lys	Phe	His	Thr	Thr	Cys	
				245										255		
TTT	GAA	GAG	GGG	ACA	GAT	GAC	ATT	CAG	GGT	GAG	TCT	CCG	GCT	CCA	TGT	1052
Phe	Glu	Glu	Gly	Thr	Asp	Asp	Ile	Gln	Gly	Glu	Ser	Pro	Ala	Pro	Cys	
			260					265					270			
GGG	ACA	GAA	GAG	CCC	GCC	CGC	ACC	TGC	CCC	AAT	GGG	ACC	AAA	TGT	CAG	1100
Gly	Thr	Glu	Glu	Pro	Ala	Arg	Thr	Cys	Pro	Asn	Gly	Thr	Lys	Cys	Gln	
		275					280					285				
CCC	TAC	TGG	GAA	GGG	CCC	AAC	AAC	GGG	ATC	ACT	CAG	TTC	GAC	AAC	ATC	1148
Pro	Tyr	Trp	Glu	Gly	Pro	Asn	Asn	Gly	Ile	Thr	Gln	Phe	Asp	Asn	Ile	
	290					295					300					
CTG	TTT	GCA	GTG	CTG	ACT	GTT	TTC	CAG	TGC	ATA	ACC	ATG	GAA	GGG	TGG	1196
Leu	Phe	Ala	Val	Leu	Thr	Val	Phe	Gln	Cys	Ile	Thr	Met	Glu	Gly	Trp	
305					310					315					320	
ACT	GAT	CTC	CTC	TAC	AAT	AGC	AAC	GAT	GCC	TCA	GGG	AAC	ACT	TGG	AAC	1244
Thr	Asp	Leu	Leu	Tyr	Asn	Ser	Asn	Asp	Ala	Ser	Gly	Asn	Thr	Trp	Asn	
				325					330					335		
TGG	TTG	TAC	TTC	ATC	CCC	CTC	ATC	ATC	ATC	GGC	TCC	TTT	TTT	ATG	CTG	1292
Trp	Leu	Tyr	Phe	Ile	Pro	Leu	Ile	Ile	Ile	Gly	Ser	Phe	Phe	Met	Leu	
			340					345					350			
AAC	CTT	GTG	CTG	GGT	GTG	CTG	TCA	GGG	GAG	TTT	GCC	AAA	GAA	AGG	GAA	1340
Asn	Leu	Val	Leu	Gly	Val	Leu	Ser	Gly	Glu	Phe	Ala	Lys	Glu	Arg	Glu	
		355					360					365				
CGG	GTG	GAG	AAC	CGG	CGG	GCT	TTT	CTG	AAG	CTG	AGG	CGG	CAA	CAA	CAG	1388
Arg	Val	Glu	Asn	Arg	Arg	Ala	Phe	Leu	Lys	Leu	Arg	Arg	Gln	Gln	Gln	
	370					375					380					
ATT	GAA	CGT	GAG	CTC	AAT	GGG	TAC	ATG	GAA	TGG	ATC	TCA	AAA	GCA	GAA	1436
Ile	Glu	Arg	Glu	Leu	Asn	Gly	Tyr	Met	Glu	Trp	Ile	Ser	Lys	Ala	Glu	
385					390					395					400	
GAG	GTG	ATC	CTC	GCC	GAG	GAT	GAA	ACT	GAC	GGG	GAG	CAG	AGG	CAT	CCC	1484
Glu	Val	Ile	Leu	Ala	Glu	Asp	Glu	Thr	Asp	Gly	Glu	Gln	Arg	His	Pro	
				405					410					415		
TTT	GAT	GGA	GCT	CTG	CGG	AGA	ACC	ACC	ATA	AAG	AAA	AGC	AAG	ACA	GAT	1532
Phe	Asp	Gly	Ala	Leu	Arg	Arg	Thr	Thr	Ile	Lys	Lys	Ser	Lys	Thr	Asp	
			420					425					430			
TTG	CTC	AAC	CCC	GAA	GAG	GCT	GAG	GAT	CAG	CTG	GCT	GAT	ATA	GCC	TCT	1580
Leu	Leu	Asn	Pro	Glu	Glu	Ala	Glu	Asp	Gln	Leu	Ala	Asp	Ile	Ala	Ser	
		435					440					445				
GTG	GGT	TCT	CCC	TTC	GCC	CGA	GCC	AGC	ATT	AAA	AGT	GCC	AAG	CTG	GAG	1628

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Val	Gly	Ser	Pro	Phe	Ala	Arg	Ala	Ser	Ile	Lys	Ser	Ala	Lys	Leu	Glu	
450						455					460					
AAC	TCG	ACC	TTT	TTT	CAC	AAA	AAG	GAG	AGG	AGG	ATG	CGT	TTC	TAC	ATC	1676
Asn	Ser	Thr	Phe	Phe	His	Lys	Lys	Glu	Arg	Arg	Met	Arg	Phe	Tyr	Ile	
465					470					475					480	
CGC	CGC	ATG	GTC	AAA	ACT	CAG	GCC	TTC	TAC	TGG	ACT	GTA	CTC	AGT	TTG	1724
Arg	Arg	Met	Val	Lys	Thr	Gln	Ala	Phe	Tyr	Trp	Thr	Val	Leu	Ser	Leu	
				485					490					495		
GTA	GCT	CTC	AAC	ACG	CTG	TGT	GTT	GCT	ATT	GTT	CAC	TAC	AAC	CAG	CCC	1772
Val	Ala	Leu	Asn	Thr	Leu	Cys	Val	Ala	Ile	Val	His	Tyr	Asn	Gln	Pro	
			500					505					510			
GAG	TGG	CTC	TCC	GAC	TTC	CTT	TAC	TAT	GCA	GAA	TTC	ATT	TTC	TTA	GGA	1820
Glu	Trp	Leu	Ser	Asp	Phe	Leu	Tyr	Tyr	Ala	Glu	Phe	Ile	Phe	Leu	Gly	
		515					520					525				
CTC	TTT	ATG	TCC	GAA	ATG	TTT	ATA	AAA	ATG	TAC	GGG	CTT	GGG	ACG	CGG	1868
Leu	Phe	Met	Ser	Glu	Met	Phe	Ile	Lys	Met	Tyr	Gly	Leu	Gly	Thr	Arg	
		530				535					540					
CCT	TAC	TTC	CAC	TCT	TCC	TTC	AAC	TGC	TTT	GAC	TGT	GGG	GTT	ATC	ATT	1916
Pro	Tyr	Phe	His	Ser	Ser	Phe	Asn	Cys	Phe	Asp	Cys	Gly	Val	Ile	Ile	
					550					555					560	
GGG	AGC	ATC	TTC	GAG	GTC	ATC	TGG	GCT	GTC	ATA	AAA	CCT	GGC	ACA	TCC	1964
Gly	Ser	Ile	Phe	Glu	Val	Ile	Trp	Ala	Val	Ile	Lys	Pro	Gly	Thr	Ser	
				565					570					575		
TTT	GGA	ATC	AGC	GTG	TTA	CGA	GCC	CTC	AGG	TTA	TTG	CGT	ATT	TTC	AAA	2012
Phe	Gly	Ile	Ser	Val	Leu	Arg	Ala	Leu	Arg	Leu	Leu	Arg	Ile	Phe	Lys	
			580					585					590			
GTC	ACA	AAG	TAC	TGG	GCA	TCT	CTC	AGA	AAC	CTG	GTC	GTC	TCT	CTC	CTC	2060
Val	Thr	Lys	Tyr	Trp	Ala	Ser	Leu	Arg	Asn	Leu	Val	Val	Ser	Leu	Leu	
		595					600					605				
AAC	TCC	ATG	AAG	TCC	ATC	ATC	AGC	CTG	TTG	TTT	CTC	CTT	TTC	CTG	TTC	2108
Asn	Ser	Met	Lys	Ser	Ile	Ile	Ser	Leu	Leu	Phe	Leu	Leu	Phe	Leu	Phe	
		610				615					620					
ATT	GTC	GTC	TTC	GCC	CTT	TTG	GGA	ATG	CAA	CTC	TTC	GGC	GGC	CAG	TTT	2156
Ile	Val	Val	Phe	Ala	Leu	Leu	Gly	Met	Gln	Leu	Phe	Gly	Gly	Gln	Phe	
					630					635					640	
AAT	TTC	GAT	GAA	GGG	ACT	CCT	CCC	ACC	AAC	TTC	GAT	ACT	TTT	CCA	GCA	2204
Asn	Phe	Asp	Glu	Gly	Thr	Pro	Pro	Thr	Asn	Phe	Asp	Thr	Phe	Pro	Ala	
				645					650					655		
GCA	ATA	ATG	ACG	GTG	TTT	CAG	ATC	CTG	ACG	GGC	GAA	GAC	TGG	AAC	GAG	2252
Ala	Ile	Met	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gly	Glu	Asp	Trp	Asn	Glu	
				660				665					670			
GTC	ATG	TAC	GAC	GGG	ATC	AAG	TCT	CAG	GGG	GGC	GTG	CAG	GGC	GGC	ATG	2300

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Val	Met	Tyr	Asp	Gly	Ile	Lys	Ser	Gln	Gly	Gly	Val	Gln	Gly	Gly	Met	
	675						680					685				
GTG	TTC	TCC	ATC	TAT	TTC	ATT	GTA	CTG	ACG	CTC	TTT	GGG	AAC	TAC	ACC	2348
Val	Phe	Ser	Ile	Tyr	Phe	Ile	Val	Leu	Thr	Leu	Phe	Gly	Asn	Tyr	Thr	
	690					695					700					
CTC	CTG	AAT	GTG	TTC	TTG	GCC	ATC	GCT	GTG	GAC	AAT	CTG	GCC	AAC	GCC	2396
Leu	Leu	Asn	Val	Phe	Leu	Ala	Ile	Ala	Val	Asp	Asn	Leu	Ala	Asn	Ala	
705					710					715					720	
CAG	GAG	CTC	ACC	AAG	GTG	GAG	GCG	GAC	GAG	CAA	GAG	GAA	GAA	GAA	GCA	2444
Gln	Glu	Leu	Thr	Lys	Val	Glu	Ala	Asp	Glu	Gln	Glu	Glu	Glu	Glu	Ala	
				725					730						735	
GCG	AAC	CAG	AAA	CTT	GCC	CTA	CAG	AAA	GCC	AAG	GAG	GTG	GCA	GAA	GTG	2492
Ala	Asn	Gln	Lys	Leu	Ala	Leu	Gln	Lys	Ala	Lys	Glu	Val	Ala	Glu	Val	
			740					745					750			
AGT	CCT	CTG	TCC	GCG	GCC	AAC	ATG	TCT	ATA	GCT	GTG	AAA	GAG	CAA	CAG	2540
Ser	Pro	Leu	Ser	Ala	Ala	Asn	Met	Ser	Ile	Ala	Val	Lys	Glu	Gln	Gln	
		755					760					765				
AAG	AAT	CAA	AAG	CCA	GCC	AAG	TCC	GTG	TGG	GAG	CAG	CGG	ACC	AGT	GAG	2588
Lys	Asn	Gln	Lys	Pro	Ala	Lys	Ser	Val	Trp	Glu	Gln	Arg	Thr	Ser	Glu	
	770					775					780					
ATG	CGA	AAG	CAG	AAC	TTG	CTG	GCC	AGC	CGG	GAG	GCC	CTG	TAT	AAC	GAA	2636
Met	Arg	Lys	Gln	Asn	Leu	Leu	Ala	Ser	Arg	Glu	Ala	Leu	Tyr	Asn	Glu	
785					790					795					800	
ATG	GAC	CCG	GAC	GAG	CGC	TGG	AAG	GCT	GCC	TAC	ACG	CGG	CAC	CTG	CGG	2684
Met	Asp	Pro	Asp	Glu	Arg	Trp	Lys	Ala	Ala	Tyr	Thr	Arg	His	Leu	Arg	
				805					810					815		
CCA	GAC	ATG	AAG	ACG	CAC	TTG	GAC	CGG	CCG	CTG	GTG	GTG	GAC	CCG	CAG	2732
Pro	Asp	Met	Lys	Thr	His	Leu	Asp	Arg	Pro	Leu	Val	Val	Asp	Pro	Gln	
			820					825					830			
GAG	AAC	CGC	AAC	AAC	AAC	ACC	AAC	AAG	AGC	CGG	GCG	GCC	GAG	CCC	ACC	2780
Glu	Asn	Arg	Asn	Asn	Asn	Thr	Asn	Lys	Ser	Arg	Ala	Ala	Glu	Pro	Thr	
		835					840					845				
GTG	GAC	CAG	CGC	CTC	GGC	CAG	CAG	CGC	GCC	GAG	GAC	TTC	CTC	AGG	AAA	2828
Val	Asp	Gln	Arg	Leu	Gly	Gln	Gln	Arg	Ala	Glu	Asp	Phe	Leu	Arg	Lys	
	850					855					860					
CAG	GCC	CGC	TAC	CAC	GAT	CGG	GCC	CGG	GAC	CCC	AGC	GGC	TCG	GCG	GGC	2876
Gln	Ala	Arg	Tyr	His	Asp	Arg	Ala	Arg	Asp	Pro	Ser	Gly	Ser	Ala	Gly	
865					870					875					880	
CTG	GAC	GCA	CGG	AGG	CCC	TGG	GCG	GGA	AGC	CAG	GAG	GCC	GAG	CTG	AGC	2924
Leu	Asp	Ala	Arg	Arg	Pro	Trp	Ala	Gly	Ser	Gln	Glu	Ala	Glu	Leu	Ser	
				885					890					895		
CGG	GAG	GGA	CCC	TAC	GGC	CGC	GAG	TCG	GAC	CAC	CAC	GCC	CGG	GAG	GGC	2972

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Arg	Glu	Gly	Pro	Tyr	Gly	Arg	Glu	Ser	Asp	His	His	Ala	Arg	Glu	Gly		
			900					905					910				
AGC	CTG	GAG	CAA	CCC	GGG	TTC	TGG	GAG	GGC	GAG	GCC	GAG	CGA	GGC	AAG		3020
Ser	Leu	Glu	Gln	Pro	Gly	Phe	Trp	Glu	Gly	Glu	Ala	Glu	Arg	Gly	Lys		
		915					920					925					
GCC	GGG	GAC	CCC	CAC	CGG	AGG	CAC	GTG	CAC	CGG	CAG	GGG	GGC	AGC	AGG		3068
Ala	Gly	Asp	Pro	His	Arg	Arg	His	Val	His	Arg	Gln	Gly	Gly	Ser	Arg		
	930					935					940						
GAG	AGC	CGC	AGC	GGG	TCC	CCG	CGC	ACG	GGC	GCG	GAC	GGG	GAG	CAT	CGA		3116
Glu	Ser	Arg	Ser	Gly	Ser	Pro	Arg	Thr	Gly	Ala	Asp	Gly	Glu	His	Arg		
945					950					955					960		
CGT	CAT	CGC	GCG	CAC	CGC	AGG	CCC	GGG	GAG	GAG	GGT	CCG	GAG	GAC	AAG		3164
Arg	His	Arg	Ala	His	Arg	Arg	Pro	Gly	Glu	Glu	Gly	Pro	Glu	Asp	Lys		
				965					970					975			
GCG	GAG	CGG	AGG	GCG	CGG	CAC	CGC	GAG	GGC	AGC	CGG	CCG	GCC	CGG	GGC		3212
Ala	Glu	Arg	Arg	Ala	Arg	His	Arg	Glu	Gly	Ser	Arg	Pro	Ala	Arg	Gly		
			980					985					990				
GGC	GAG	GGC	GAG	GGC	GAG	GGC	CCC	GAC	GGG	GGC	GAG	CGC	AGG	AGA	AGG		3260
Gly	Glu	Gly	Glu	Gly	Glu	Gly	Pro	Asp	Gly	Gly	Glu	Arg	Arg	Arg	Arg		
		995					1000					1005					
CAC	CGG	CAT	GGC	GCT	CCA	GCC	ACG	TAC	GAG	GGG	GAC	GCG	CGG	AGG	GAG		3308
His	Arg	His	Gly	Ala	Pro	Ala	Thr	Tyr	Glu	Gly	Asp	Ala	Arg	Arg	Glu		
	1010					1015					1020						
GAC	AAG	GAG	CGG	AGG	CAT	CGG	AGG	AGG	AAA	GAG	AAC	CAG	GGC	TCC	GGG		3356
Asp	Lys	Glu	Arg	Arg	His	Arg	Arg	Arg	Lys	Glu	Asn	Gln	Gly	Ser	Gly		
1025					1030				1035						1040		
GTC	CCT	GTG	TCG	GGC	CCC	AAC	CTG	TCA	ACC	ACC	CGG	CCA	ATC	CAG	CAG		3404
Val	Pro	Val	Ser	Gly	Pro	Asn	Leu	Ser	Thr	Thr	Arg	Pro	Ile	Gln	Gln		
				1045					1050					1055			
GAC	CTG	GGC	CGC	CAA	GAC	CCA	CCC	CTG	GCA	GAG	GAT	ATT	GAC	AAC	ATG		3452
Asp	Leu	Gly	Arg	Gln	Asp	Pro	Pro	Leu	Ala	Glu	Asp	Ile	Asp	Asn	Met		
			1060					1065				1070					
AAG	AAC	AAC	AAG	CTG	GCC	ACC	GCG	GAG	TCG	GCC	GCT	CCC	CAC	GGC	AGC		3500
Lys	Asn	Asn	Lys	Leu	Ala	Thr	Ala	Glu	Ser	Ala	Ala	Pro	His	Gly	Ser		
		1075					1080					1085					
CTT	GGC	CAC	GCC	GGC	CTG	CCC	CAG	AGC	CCA	GCC	AAG	ATG	GGA	AAC	AGC		3548
Leu	Gly	His	Ala	Gly	Leu	Pro	Gln	Ser	Pro	Ala	Lys	Met	Gly	Asn	Ser		
	1090					1095					1100						
ACC	GAC	CCC	GGC	CCC	ATG	CTG	GCC	ATC	CCT	GCC	ATG	GCC	ACC	AAC	CCC		3596
Thr	Asp	Pro	Gly	Pro	Met	Leu	Ala	Ile	Pro	Ala	Met	Ala	Thr	Asn	Pro		
1105					1110				1115						1120		
CAG	AAC	GCC	GCC	AGC	CGC	CGG	ACG	CCC	AAC	AAC	CCG	GGG	AAC	CCA	TCC		3644

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Gln	Asn	Ala	Ala	Ser	Arg	Arg	Thr	Pro	Asn	Asn	Pro	Gly	Asn	Pro	Ser	
				1125					1130					1135		
AAT	CCC	GGC	CCC	CCC	AAG	ACC	CCC	GAG	AAT	AGC	CTT	ATC	GTC	ACC	AAC	3692
Asn	Pro	Gly	Pro	Pro	Lys	Thr	Pro	Glu	Asn	Ser	Leu	Ile	Val	Thr	Asn	
			1140					1145					1150			
CCC	AGC	GGC	ACC	CAG	ACC	AAT	TCA	GCT	AAG	ACT	GCC	AGG	AAA	CCC	GAC	3740
Pro	Ser	Gly	Thr	Gln	Thr	Asn	Ser	Ala	Lys	Thr	Ala	Arg	Lys	Pro	Asp	
			1155				1160					1165				
CAC	ACC	ACA	GTG	GAC	ATC	CCC	CCA	GCC	TGC	CCA	CCC	CCC	CTC	AAC	CAC	3788
His	Thr	Thr	Val	Asp	Ile	Pro	Pro	Ala	Cys	Pro	Pro	Pro	Leu	Asn	His	
	1170					1175					1180					
ACC	GTC	GTA	CAA	GTG	AAC	AAA	AAC	GCC	AAC	CCA	GAC	CCA	CTG	CCA	AAA	3836
Thr	Val	Val	Gln	Val	Asn	Lys	Asn	Ala	Asn	Pro	Asp	Pro	Leu	Pro	Lys	
1185					1190					1195					1200	
AAA	GAG	GAA	GAG	AAG	AAG	GAG	GAG	GAG	GAA	GAC	GAC	CGT	GGG	GAA	GAC	3884
Lys	Glu	Glu	Glu	Lys	Lys	Glu	Glu	Glu	Glu	Asp	Asp	Arg	Gly	Glu	Asp	
				1205					1210					1215		
GGC	CCT	AAG	CCA	ATG	CCT	CCC	TAT	AGC	TCC	ATG	TTC	ATC	CTG	TCC	ACG	3932
Gly	Pro	Lys	Pro	Met	Pro	Pro	Tyr	Ser	Ser	Met	Phe	Ile	Leu	Ser	Thr	
			1220					1225					1230			
ACC	AAC	CCC	CTT	CGC	CGC	CTG	TGC	CAT	TAC	ATC	CTG	AAC	CTG	CGC	TAC	3980
Thr	Asn	Pro	Leu	Arg	Arg	Leu	Cys	His	Tyr	Ile	Leu	Asn	Leu	Arg	Tyr	
		1235				1240						1245				
TTT	GAG	ATG	TGC	ATC	CTC	ATG	GTC	ATT	GCC	ATG	AGC	AGC	ATC	GCC	CTG	4028
Phe	Glu	Met	Cys	Ile	Leu	Met	Val	Ile	Ala	Met	Ser	Ser	Ile	Ala	Leu	
	1250					1255					1260					
GCC	GCC	GAG	GAC	CCT	GTG	CAG	CCC	AAC	GCA	CCT	CGG	AAC	AAC	GTG	CTG	4076
Ala	Ala	Glu	Asp	Pro	Val	Gln	Pro	Asn	Ala	Pro	Arg	Asn	Asn	Val	Leu	
1265					1270					1275					1280	
CGA	TAC	TTT	GAC	TAC	GTT	TTT	ACA	GGC	GTC	TTC	ACC	TTT	GAG	ATG	GTG	4124
Arg	Tyr	Phe	Asp	Tyr	Val	Phe	Thr	Gly	Val	Phe	Thr	Phe	Glu	Met	Val	
				1285					1290					1295		
ATC	AAG	ATG	ATT	GAC	CTG	GGG	CTC	GTC	CTG	CAT	CAG	GGT	GCC	TAC	TTC	4172
Ile	Lys	Met	Ile	Asp	Leu	Gly	Leu	Val	Leu	His	Gln	Gly	Ala	Tyr	Phe	
			1300					1305					1310			
CGT	GAC	CTC	TGG	AAT	ATT	CTC	GAC	TTC	ATA	GTG	GTC	AGT	GGG	GCC	CTG	4220
Arg	Asp	Leu	Trp	Asn	Ile	Leu	Asp	Phe	Ile	Val	Val	Ser	Gly	Ala	Leu	
			1315				1320					1325				
GTA	GCC	TTT	GCC	TTC	ACT	GGC	AAT	AGC	AAA	GGA	AAA	GAC	ATC	AAC	ACG	4268
Val	Ala	Phe	Ala	Phe	Thr	Gly	Asn	Ser	Lys	Gly	Lys	Asp	Ile	Asn	Thr	
	1330					1335					1340					
ATT	AAA	TCC	CTC	CGA	GTC	CTC	CGG	GTG	CTA	CGA	CCT	CTT	AAA	ACC	ATC	4316

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Ile Lys Ser Leu Arg Val Leu Arg Val Leu Arg Pro Leu Lys Thr Ile	
1345 1350 1355 1360	
AAG CGG CTG CCA AAG CTC AAG GCT GTG TTT GAC TGT GTG GTG AAC TCA	4364
Lys Arg Leu Pro Lys Leu Lys Ala Val Phe Asp Cys Val Val Asn Ser	
1365 1370 1375	
CTT AAA AAC GTC TTC AAC ATC CTC ATC GTC TAC ATG CTA TTC ATG TTC	4412
Leu Lys Asn Val Phe Asn Ile Leu Ile Val Tyr Met Leu Phe Met Phe	
1380 1385 1390	
ATC TTC GCC GTG GTG GCT GTG CAG CTC TTC AAG GGG AAA TTC TTC CAC	4460
Ile Phe Ala Val Val Ala Val Gln Leu Phe Lys Gly Lys Phe Phe His	
1395 1400 1405	
TGC ACT GAC GAG TCC AAA GAG TTT GAG AAA GAT TGT CGA GGC AAA TAC	4508
Cys Thr Asp Glu Ser Lys Glu Phe Glu Lys Asp Cys Arg Gly Lys Tyr	
1410 1415 1420	
CTC CTC TAC GAG AAG AAT GAG GTG AAG GCG CGA GAC CGG GAG TGG AAG	4556
Leu Leu Tyr Glu Lys Asn Glu Val Lys Ala Arg Asp Arg Glu Trp Lys	
1425 1430 1435 1440	
AAG TAT GAA TTC CAT TAC GAC AAT GTG CTG TGG GCT CTG CTG ACC CTC	4604
Lys Tyr Glu Phe His Tyr Asp Asn Val Leu Trp Ala Leu Leu Thr Leu	
1445 1450 1455	
TTC ACC GTG TCC ACG GGA GAA GGC TGG CCA CAG GTC CTC AAG CAT TCG	4652
Phe Thr Val Ser Thr Gly Glu Gly Trp Pro Gln Val Leu Lys His Ser	
1460 1465 1470	
GTG GAC GCC ACC TTT GAG AAC CAG GGC CCC AGC CCC GGG TAC CGC ATG	4700
Val Asp Ala Thr Phe Glu Asn Gln Gly Pro Ser Pro Gly Tyr Arg Met	
1475 1480 1485	
GAG ATG TCC ATT TTC TAC GTC GTC TAC TTT GTG GTG TTC CCC TTC TTC	4748
Glu Met Ser Ile Phe Tyr Val Val Tyr Phe Val Val Phe Pro Phe Phe	
1490 1495 1500	
TTT GTC AAT ATC TTT GTG GCC TTG ATC ATC ATC ACC TTC CAG GAG CAA	4796
Phe Val Asn Ile Phe Val Ala Leu Ile Ile Ile Thr Phe Gln Glu Gln	
1505 1510 1515 1520	
GGG GAC AAG ATG ATG GAG GAA TAC AGC CTG GAG AAA AAT GAG AGG GCC	4844
Gly Asp Lys Met Met Glu Glu Tyr Ser Leu Glu Lys Asn Glu Arg Ala	
1525 1530 1535	
TGC ATT GAT TTC GCC ATC AGC GCC AAG CCG CTG ACC CGA CAC ATG CCG	4892
Cys Ile Asp Phe Ala Ile Ser Ala Lys Pro Leu Thr Arg His Met Pro	
1540 1545 1550	
CAG AAC AAG CAG AGC TTC CAG TAC CGC ATG TGG CAG TTC GTG GTG TCT	4940
Gln Asn Lys Gln Ser Phe Gln Tyr Arg Met Trp Gln Phe Val Val Ser	
1555 1560 1565	
CCG CCT TTC GAG TAC ACG ATC ATG GCC ATG ATC GCC CTC AAC ACC ATC	4988

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Pro	Pro	Phe	Glu	Tyr	Thr	Ile	Met	Ala	Met	Ile	Ala	Leu	Asn	Thr	Ile		
1570						1575					1580						
GTG	CTT	ATG	ATG	AAG	TTC	TAT	GGG	GCT	TCT	GTT	GCT	TAT	GAA	AAT	GCC	5036	
Val	Leu	Met	Met	Lys	Phe	Tyr	Gly	Ala	Ser	Val	Ala	Tyr	Glu	Asn	Ala	1585	1600
1585					1590					1595							
CTG	CGG	GTG	TTC	AAC	ATC	GTC	TTC	ACC	TCC	CTC	TTC	TCT	CTG	GAA	TGT	5084	
Leu	Arg	Val	Phe	Asn	Ile	Val	Phe	Thr	Ser	Leu	Phe	Ser	Leu	Glu	Cys	1605	1615
				1605					1610								
GTG	CTG	AAA	GTC	ATG	GCT	TTT	GGG	ATT	CTG	AAT	TAT	TTC	CGC	GAT	GCC	5132	
Val	Leu	Lys	Val	Met	Ala	Phe	Gly	Ile	Leu	Asn	Tyr	Phe	Arg	Asp	Ala	1620	1630
			1620					1625									
TGG	AAC	ATC	TTC	GAC	TTT	GTG	ACT	GTT	CTG	GGC	AGC	ATC	ACC	GAT	ATC	5180	
Trp	Asn	Ile	Phe	Asp	Phe	Val	Thr	Val	Leu	Gly	Ser	Ile	Thr	Asp	Ile	1635	1645
		1635					1640					1645					
CTC	GTG	ACT	GAG	TTT	GGG	AAT	CCG	AAT	AAC	TTC	ATC	AAC	CTG	AGC	TTT	5228	
Leu	Val	Thr	Glu	Phe	Gly	Asn	Pro	Asn	Asn	Phe	Ile	Asn	Leu	Ser	Phe	1650	1660
	1650					1655						1660					
CTC	CGC	CTC	TTC	CGA	GCT	GCC	CGG	CTC	ATC	AAA	CTT	CTC	CGT	CAG	GGT	5276	
Leu	Arg	Leu	Phe	Arg	Ala	Ala	Arg	Leu	Ile	Lys	Leu	Leu	Arg	Gln	Gly	1665	1680
	1665				1670					1675							
TAC	ACC	ATC	CGC	ATT	CTT	CTC	TGG	ACC	TTT	GTG	CAG	TCC	TTC	AAG	GCC	5324	
Tyr	Thr	Ile	Arg	Ile	Leu	Leu	Trp	Thr	Phe	Val	Gln	Ser	Phe	Lys	Ala	1685	1695
				1685					1690								
CTG	CCT	TAT	GTC	TGT	CTG	CTG	ATC	GCC	ATG	CTC	TTC	TTC	ATC	TAT	GCC	5372	
Leu	Pro	Tyr	Val	Cys	Leu	Leu	Ile	Ala	Met	Leu	Phe	Phe	Ile	Tyr	Ala	1700	1710
			1700					1705					1710				
ATC	ATT	GGG	ATG	CAG	GTG	TTT	GGT	AAC	ATT	GGC	ATC	GAC	GTG	GAG	GAC	5420	
Ile	Ile	Gly	Met	Gln	Val	Phe	Gly	Asn	Ile	Gly	Ile	Asp	Val	Glu	Asp	1715	1725
		1715					1720					1725					
GAG	GAC	AGT	GAT	GAA	GAT	GAG	TTC	CAA	ATC	ACT	GAG	CAC	AAT	AAC	TTC	5468	
Glu	Asp	Ser	Asp	Glu	Asp	Glu	Phe	Gln	Ile	Thr	Glu	His	Asn	Asn	Phe	1730	1740
		1730				1735					1740						
CGG	ACC	TTC	TTC	CAG	GCC	CTC	ATG	CTT	CTC	TTC	CGG	AGT	GCC	ACC	GGG	5516	
Arg	Thr	Phe	Phe	Gln	Ala	Leu	Met	Leu	Leu	Phe	Arg	Ser	Ala	Thr	Gly	1745	1760
				1750						1755							
GAA	GCT	TGG	CAC	AAC	ATC	ATG	CTT	TCC	TGC	CTC	AGC	GGG	AAA	CCG	TGT	5564	
Glu	Ala	Trp	His	Asn	Ile	Met	Leu	Ser	Cys	Leu	Ser	Gly	Lys	Pro	Cys	1765	1775
				1765					1770					1775			
GAT	AAG	AAC	TCT	GGC	ATC	CTG	ACT	CGA	GAG	TGT	GGC	AAT	GAA	TTT	GCT	5612	
Asp	Lys	Asn	Ser	Gly	Ile	Leu	Thr	Arg	Glu	Cys	Gly	Asn	Glu	Phe	Ala	1780	1790
			1780					1785					1790				
TAT	TTT	TAC	TTT	GTT	TCC	TTC	ATC	TTC	CTC	TGC	TCG	TTT	CTG	ATG	CTG	5660	

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Tyr	Phe	Tyr	Phe	Val	Ser	Phe	Ile	Phe	Leu	Cys	Ser	Phe	Leu	Met	Leu		
		1795					1800					1805					
AAT	CTC	TTT	GTC	GCC	GTC	ATC	ATG	GAC	AAC	TTT	GAG	TAC	CTC	ACC	CGA	5708	
Asn	Leu	Phe	Val	Ala	Val	Ile	Met	Asp	Asn	Phe	Glu	Tyr	Leu	Thr	Arg		
	1810					1815					1820						
GAC	TCC	TCC	ATC	CTG	GGC	CCC	CAC	CAC	CTG	GAT	GAG	TAC	GTG	CGT	GTC	5756	
Asp	Ser	Ser	Ile	Leu	Gly	Pro	His	His	Leu	Asp	Glu	Tyr	Val	Arg	Val		
	1825				1830					1835					1840		
TGG	GCC	GAG	TAT	GAC	CCC	GCA	GCT	TGG	GGC	CGC	ATG	CCT	TAC	CTG	GAC	5804	
Trp	Ala	Glu	Tyr	Asp	Pro	Ala	Ala	Trp	Gly	Arg	Met	Pro	Tyr	Leu	Asp		
				1845					1850					1855			
ATG	TAT	CAG	ATG	CTG	AGA	CAC	ATG	TCT	CCG	CCC	CTG	GGT	CTG	GGG	AAG	5852	
Met	Tyr	Gln	Met	Leu	Arg	His	Met	Ser	Pro	Pro	Leu	Gly	Leu	Gly	Lys		
			1860					1865					1870				
AAG	TGT	CCG	GCC	AGA	GTG	GCT	TAC	AAG	CGG	CTT	CTG	CGG	ATG	GAC	CTG	5900	
Lys	Cys	Pro	Ala	Arg	Val	Ala	Tyr	Lys	Arg	Leu	Leu	Arg	Met	Asp	Leu		
		1875					1880					1885					
CCC	GTC	GCA	GAT	GAC	AAC	ACC	GTC	CAC	TTC	AAT	TCC	ACC	CTC	ATG	GCT	5948	
Pro	Val	Ala	Asp	Asp	Asn	Thr	Val	His	Phe	Asn	Ser	Thr	Leu	Met	Ala		
	1890					1895					1900						
CTG	ATC	CGC	ACA	GCC	CTG	GAC	ATC	AAG	ATT	GCC	AAG	GGA	GGA	GCC	GAC	5996	
Leu	Ile	Arg	Thr	Ala	Leu	Asp	Ile	Lys	Ile	Ala	Lys	Gly	Gly	Ala	Asp		
	1905				1910					1915					1920		
AAA	CAG	CAG	ATG	GAC	GCT	GAG	CTG	CGG	AAG	GAG	ATG	ATG	GCG	ATT	TGG	6044	
Lys	Gln	Gln	Met	Asp	Ala	Glu	Leu	Arg	Lys	Glu	Met	Met	Ala	Ile	Trp		
			1925						1930					1935			
CCC	AAT	CTG	TCC	CAG	AAG	ACG	CTA	GAC	CTG	CTG	GTC	ACA	CCT	CAC	AAG	6092	
Pro	Asn	Leu	Ser	Gln	Lys	Thr	Leu	Asp	Leu	Leu	Val	Thr	Pro	His	Lys		
			1940					1945					1950				
TCC	ACG	GAC	CTC	ACC	GTG	GGG	AAG	ATC	TAC	GCA	GCC	ATG	ATG	ATC	ATG	6140	
Ser	Thr	Asp	Leu	Thr	Val	Gly	Lys	Ile	Tyr	Ala	Ala	Met	Met	Ile	Met		
		1955				1960						1965					
GAG	TAC	TAC	CGG	CAG	AGC	AAG	GCC	AAG	AAG	CTG	CAG	GCC	ATG	CGC	GAG	6188	
Glu	Tyr	Tyr	Arg	Gln	Ser	Lys	Ala	Lys	Lys	Leu	Gln	Ala	Met	Arg	Glu		
	1970					1975					1980						
GAG	CAG	GAC	CGG	ACA	CCC	CTC	ATG	TTC	CAG	CGC	ATG	GAG	CCC	CCG	TCC	6236	
Glu	Gln	Asp	Arg	Thr	Pro	Leu	Met	Phe	Gln	Arg	Met	Glu	Pro	Pro	Ser		
	1985				1990					1995					2000		
CCA	ACG	CAG	GAA	GGG	GGA	CCT	GGC	CAG	AAC	GCC	CTC	CCC	TCC	ACC	CAG	6284	
Pro	Thr	Gln	Glu	Gly	Gly	Pro	Gly	Gln	Asn	Ala	Leu	Pro	Ser	Thr	Gln		
				2005					2010					2015			
CTG	GAC	CCA	GGA	GGA	GCC	CTG	ATG	GCT	CAC	GAA	AGC	GGC	CTC	AAG	GAG	6332	

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Leu	Asp	Pro	Gly	Gly	Ala	Leu	Met	Ala	His	Glu	Ser	Gly	Leu	Lys	Glu	
			2020					2025					2030			
AGC	CCG	TCC	TGG	GTG	ACC	CAG	CGT	GCC	CAG	GAG	ATG	TTC	CAG	AAG	ACG	6380
Ser	Pro	Ser	Trp	Val	Thr	Gln	Arg	Ala	Gln	Glu	Met	Phe	Gln	Lys	Thr	
		2035					2040					2045				
GGC	ACA	TGG	AGT	CCG	GAA	CAA	GGC	CCC	CCT	ACC	GAC	ATG	CCC	AAC	AGC	6428
Gly	Thr	Trp	Ser	Pro	Glu	Gln	Gly	Pro	Pro	Thr	Asp	Met	Pro	Asn	Ser	
	2050					2055					2060					
CAG	CCT	AAC	TCT	CAG	TCC	GTG	GAG	ATG	CGA	GAG	ATG	GGC	AGA	GAT	GGC	6476
Gln	Pro	Asn	Ser	Gln	Ser	Val	Glu	Met	Arg	Glu	Met	Gly	Arg	Asp	Gly	
2065					2070					2075					2080	
TAC	TCC	GAC	AGC	GAG	CAC	TAC	CTC	CCC	ATG	GAA	GGC	CAG	GGC	CGG	GCT	6524
Tyr	Ser	Asp	Ser	Glu	His	Tyr	Leu	Pro	Met	Glu	Gly	Gln	Gly	Arg	Ala	
				2085					2090					2095		
GCC	TCC	ATG	CCC	CGC	CTC	CCT	GCA	GAG	AAC	CAG	AGG	AGA	AGG	GGC	CGG	6572
Ala	Ser	Met	Pro	Arg	Leu	Pro	Ala	Glu	Asn	Gln	Arg	Arg	Arg	Gly	Arg	
			2100					2105					2110			
CCA	CGT	GGG	AAT	AAC	CTC	AGT	ACC	ATC	TCA	GAC	ACC	AGC	CCC	ATG	AAG	6620
Pro	Arg		Asn	Asn	Leu	Ser	Thr	Ile	Ser	Asp	Thr	Ser	Pro	Met	Lys	
	2115						2120					2125				
CGT	TCA	GCC	TCC	GTG	CTG	GGC	CCC	AAG	GCC	CGA	CGC	CTG	GAC	GAT	TAC	6668
Arg	Ser	Ala	Ser	Val	Leu	Gly	Pro	Lys	Ala	Arg	Arg	Leu	Asp	Asp	Tyr	
	2130					2135					2140					
TCG	CTG	GAG	CGG	GTC	CCG	CCC	GAG	GAG	AAC	CAG	CGG	CAC	CAC	CAG	CGG	6716
Ser	Leu	Glu	Arg	Val	Pro	Pro	Glu	Glu	Asn	Gln	Arg	His	His	Gln	Arg	
2145					2150				2155					2160		
CGC	CGC	GAC	CGC	AGC	CAC	CGC	GCC	TCT	GAG	CGC	TCC	CTG	GGC	CGC	TAC	6764
Arg	Arg	Asp	Arg	Ser	His	Arg	Ala	Ser	Glu	Arg	Ser	Leu	Gly	Arg	Tyr	
				2165					2170					2175		
ACC	GAT	GTG	GAC	ACA	GGC	TTG	GGG	ACA	GAC	CTG	AGC	ATG	ACC	ACC	CAA	6812
Thr	Asp	Val	Asp	Thr	Gly	Leu	Gly	Thr	Asp	Leu	Ser	Met	Thr	Thr	Gln	
			2180					2185					2190			
TCC	GGG	GAC	CTG	CCG	TCG	AAG	GAG	CGG	GAC	CAG	GAG	CGG	GGC	CGG	CCC	6860
Ser	Gly	Asp	Leu	Pro	Ser	Lys	Glu	Arg	Asp	Gln	Glu	Arg	Gly	Arg	Pro	
	2195						2200					2205				
AAG	GAT	CGG	AAG	CAT	CGA	CAG	CAC	CAC	CAC	CAC	CAC	CAC	CAC	CAC	CAC	6908
Lys	Asp	Arg	Lys	His	Arg	Gln	His	His	His	His	His	His	His	His	His	
	2210					2215					2220					
CAT	CCC	CCG	CCC	CCC	GAC	AAG	GAC	CGC	TAT	GCC	CAG	GAA	CGG	CCG	GAC	6956
His	Pro	Pro	Pro	Pro	Asp	Lys	Asp	Arg	Tyr	Ala	Gln	Glu	Arg	Pro	Asp	
2225					2230					2235				2240		
CAC	GGC	CGG	GCA	CGG	GCT	CGG	GAC	CAG	CGC	TGG	TCC	CGC	TCG	CCC	AGC	7004

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His	Gly	Arg	Ala	Arg	Ala	Arg	Asp	Gln	Arg	Trp	Ser	Arg	Ser	Pro	Ser		
				2245					2250					2255			
GAG	GGC	CGA	GAG	CAC	ATG	GCG	CAC	CGG	CAG	GGC	AGT	AGT	TCC	GTA	AGT	7052	
Glu	Gly	Arg	Glu	His	Met	Ala	His	Arg	Gln	Gly	Ser	Ser	Ser	Val	Ser		
			2260					2265					2270				
GGA	AGC	CCA	GCC	CCC	TCA	ACA	TCT	GGT	ACC	AGC	ACT	CCG	CGG	CGG	GGC	7100	
Gly	Ser	Pro	Ala	Pro	Ser	Thr	Ser	Gly	Thr	Ser	Thr	Pro	Arg	Arg	Gly		
		2275					2280					2285					
CGC	CGC	CAG	CTC	CCC	CAG	ACC	CCC	TCC	ACC	CCC	CGG	CCA	CAC	GTG	TCC	7148	
Arg	Arg	Gln	Leu	Pro	Gln	Thr	Pro	Ser	Thr	Pro	Arg	Pro	His	Val	Ser		
		2290				2295					2300						
TAT	TCC	CCT	GTG	ATC	CGT	AAG	GCC	GGC	GGC	TCG	GGG	CCC	CCG	CAG	CAG	7196	
Tyr	Ser	Pro	Val	Ile	Arg	Lys	Ala	Gly	Gly	Ser	Gly	Pro	Pro	Gln	Gln		
2305					2310					2315				2320			
CAG	CAG	CAG	CAG	CAG	CAG	CAG	CAG	CAG	GCG	GTG	GCC	AGG	CCG	GGC	CGG	7244	
Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Ala	Val	Ala	Arg	Pro	Gly	Arg		
				2325					2330					2335			
GCG	GCC	ACC	AGC	GGC	CCT	CGG	AGG	TAC	CCA	GGC	CCC	ACG	GCC	GAG	CCT	7292	
Ala	Ala	Thr	Ser	Gly	Pro	Arg	Arg	Tyr	Pro	Gly	Pro	Thr	Ala	Glu	Pro		
			2340					2345					2350				
CTG	GCC	GGA	GAT	CGG	CCG	CCC	ACG	GGG	GGC	CAC	AGC	AGC	GGC	CGC	TCG	7340	
Leu	Ala	Gly	Asp	Arg	Pro	Pro	Thr	Gly	Gly	His	Ser	Ser	Gly	Arg	Ser		
		2355					2360					2365					
CCC	AGG	ATG	GAG	AGG	CGG	GTC	CCA	GGC	CCG	GCC	CGG	AGC	GAG	TCC	CCC	7388	
Pro	Arg	Met	Glu	Arg	Arg	Val	Pro	Gly	Pro	Ala	Arg	Ser	Glu	Ser	Pro		
		2370				2375					2380						
AGG	GCC	TGT	CGA	CAC	GGC	GGG	GCC	CGG	TGG	CCG	GCA	TCT	GGC	CCG	CAC	7436	
Arg	Ala	Cys	Arg	His	Gly	Gly	Ala	Arg	Trp	Pro	Ala	Ser	Gly	Pro	His		
2385					2390					2395				2400			
GTG	TCC	GAG	GGG	CCC	CCG	GGT	CCC	CGG	CAC	CAT	GGC	TAC	TAC	CGG	GGC	7484	
Val	Ser	Glu	Gly	Pro	Pro	Gly	Pro	Arg	His	His	Gly	Tyr	Tyr	Arg	Gly		
				2405					2410					2415			
TCC	GAC	TAC	GAC	GAG	GCC	GAT	GGC	CCG	GGC	AGC	GGG	GGC	GGC	GAG	GAG	7532	
Ser	Asp	Tyr	Asp	Glu	Ala	Asp	Gly	Pro	Gly	Ser	Gly	Gly	Gly	Glu	Glu		
			2420					2425					2430				
GCC	ATG	GCC	GGG	GCC	TAC	GAC	GCG	CCA	CCC	CCC	GTA	CGA	CAC	GCG	TCC	7580	
Ala	Met	Ala	Gly	Ala	Tyr	Asp	Ala	Pro	Pro	Pro	Val	Arg	His	Ala	Ser		
		2435					2440					2445					
TCG	GGC	GCC	ACC	GGG	CGC	TCG	CCC	AGG	ACT	CCC	CGG	GCC	TCG	GGC	CCG	7628	
Ser	Gly	Ala	Thr	Gly	Arg	Ser	Pro	Arg	Thr	Pro	Arg	Ala	Ser	Gly	Pro		
	2450					2455					2460						
GCC	TGC	GCC	TCG	CCT	TCT	CGG	CAC	GGC	CGG	CGA	CTC	CCC	AAC	GGC	TAC	7676	

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Ala Cys Ala Ser Pro Ser Arg His Gly Arg Arg Leu Pro Asn Gly Tyr
 2465 2470 2475 2480

TAC CCG GCG CAC GGA CTG GCC AGG CCC CGC GGG CCG GGC TCC AGG AAG 7724
 Tyr Pro Ala His Gly Leu Ala Arg Pro Arg Gly Pro Gly Ser Arg Lys
 2485 2490 2495

GGC CTG CAC GAA CCC TAC AGC GAG AGT GAC GAT GAT TGG TGC TAAGCCCGGG 7776
 Gly Leu His Glu Pro Tyr Ser Glu Ser Asp Asp Asp Trp Cys
 2500 2505 2510

CGAGGTGGCG CCCGCCCGGC CCCCCACGCA CC 7808

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7791 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 237..7037
- (D) OTHER INFORMATION: /standard_name= "Alpha-1A-2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GATGTCCCGA GCTGCTATCC CCGGCTCGGC CCGGGCAGCC GCCTTCTGAG CCCCCGACCC 60

GAGGCGCCGA GCCGCCGCCG CCCGATGGGC TGGGCCGTGG AGCGTCTCCG CAGTCGTAGC 120

TCCAGCCGCC GCGTCCCAG CCCCGGCAGC CTCAGCATCA GCGCGGCGG CGGCGGCGGC 180

GGCGTCTTCC GCATCGTTCC CCGCAGCGTA ACCCGGAGCC CTTTGCTCTT TGCAGA 236

ATG GCC CGC TTC GGA GAC GAG ATG CCG GCC CGC TAC GGG GGA GGA GGC 284
 Met Ala Arg Phe Gly Asp Glu Met Pro Ala Arg Tyr Gly Gly Gly Gly
 1 5 10 15

TCC GGG GCA GCC GCC GGG GTG GTC GTG GGC AGC GGA GGC GGG CGA GGA 332
 Ser Gly Ala Ala Ala Gly Val Val Val Gly Ser Gly Gly Gly Arg Gly
 20 25 30

GCC GGG GGC AGC CGG CAG GGC GGG CAG CCC GGG GCG CAA AGG ATG TAC 380
 Ala Gly Gly Ser Arg Gln Gly Gly Gln Pro Gly Ala Gln Arg Met Tyr
 35 40 45

AAG CAG TCA ATG GCG CAG AGA GCG CGG ACC ATG GCA CTC TAC AAC CCC 428
 Lys Gln Ser Met Ala Gln Arg Ala Arg Thr Met Ala Leu Tyr Asn Pro
 50 55 60

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ATC	CCC	GTC	CGA	CAG	AAC	TGC	CTC	ACG	GTT	AAC	CGG	TCT	CTC	TTC	CTC	476
Ile	Pro	Val	Arg	Gln	Asn	Cys	Leu	Thr	Val	Asn	Arg	Ser	Leu	Phe	Leu	
65					70					75					80	
TTC	AGC	GAA	GAC	AAC	GTG	GTG	AGA	AAA	TAC	GCC	AAA	AAG	ATC	ACC	GAA	524
Phe	Ser	Glu	Asp	Asn	Val	Val	Arg	Lys	Tyr	Ala	Lys	Lys	Ile	Thr	Glu	
				85					90					95		
TGG	CCT	CCC	TTT	GAA	TAT	ATG	ATT	TTA	GCC	ACC	ATC	ATA	GCG	AAT	TGC	572
Trp	Pro	Pro	Phe	Glu	Tyr	Met	Ile	Leu	Ala	Thr	Ile	Ile	Ala	Asn	Cys	
			100					105					110			
ATC	GTC	CTC	GCA	CTG	GAG	CAG	CAT	CTG	CCT	GAT	GAT	GAC	AAG	ACC	CCG	620
Ile	Val	Leu	Ala	Leu	Glu	Gln	His	Leu	Pro	Asp	Asp	Asp	Lys	Thr	Pro	
		115					120					125				
ATG	TCT	GAA	CGG	CTG	GAT	GAC	ACA	GAA	CCA	TAC	TTC	ATT	GGA	ATT	TTT	668
Met	Ser	Glu	Arg	Leu	Asp	Asp	Thr	Glu	Pro	Tyr	Phe	Ile	Gly	Ile	Phe	
	130					135					140					
TGT	TTC	GAG	GCT	GGA	ATT	AAA	ATC	ATT	GCC	CTT	GGG	TTT	GCC	TTC	CAC	716
Cys	Phe	Glu	Ala	Gly	Ile	Lys	Ile	Ile	Ala	Leu	Gly	Phe	Ala	Phe	His	
145					150				155						160	
AAA	GGC	TCC	TAC	TTG	AGG	AAT	GGC	TGG	AAT	GTC	ATG	GAC	TTT	GTG	GTG	764
Lys	Gly	Ser	Tyr	Leu	Arg	Asn	Gly	Trp	Asn	Val	Met	Asp	Phe	Val	Val	
				165				170						175		
GTG	CTA	ACG	GGC	ATC	TTG	GCG	ACA	GTT	GGG	ACG	GAG	TTT	GAC	CTA	CGG	812
Val	Leu	Thr	Gly	Ile	Leu	Ala	Thr	Val	Gly	Thr	Glu	Phe	Asp	Leu	Arg	
			180					185					190			
ACG	CTG	AGG	GCA	GTT	CGA	GTG	CTG	CGG	CCG	CTC	AAG	CTG	GTG	TCT	GGA	860
Thr	Leu	Arg	Ala	Val	Arg	Val	Leu	Arg	Pro	Leu	Lys	Leu	Val	Ser	Gly	
		195					200					205				
ATC	CCA	AGT	TTA	CAA	GTC	GTC	CTG	AAG	TCG	ATC	ATG	AAG	GCG	ATG	ATC	908
Ile	Pro	Ser	Leu	Gln	Val	Val	Leu	Lys	Ser	Ile	Met	Lys	Ala	Met	Ile	
	210					215					220					
CCT	TTG	CTG	CAG	ATC	GGC	CTC	CTC	CTA	TTT	TTT	GCA	ATC	CTT	ATT	TTT	956
Pro	Leu	Leu	Gln	Ile	Gly	Leu	Leu	Leu	Phe	Phe	Ala	Ile	Leu	Ile	Phe	
225					230				235						240	
GCA	ATC	ATA	GGG	TTA	GAA	TTT	TAT	ATG	GGA	AAA	TTT	CAT	ACC	ACC	TGC	1004
Ala	Ile	Ile	Gly	Leu	Glu	Phe	Tyr	Met	Gly	Lys	Phe	His	Thr	Thr	Cys	
				245					250					255		
TTT	GAA	GAG	GGG	ACA	GAT	GAC	ATT	CAG	GGT	GAG	TCT	CCG	GCT	CCA	TGT	1052
Phe	Glu	Glu	Gly	Thr	Asp	Asp	Ile	Gln	Gly	Glu	Ser	Pro	Ala	Pro	Cys	
			260					265					270			
GGG	ACA	GAA	GAG	CCC	GCC	CGC	ACC	TGC	CCC	AAT	GGG	ACC	AAA	TGT	CAG	1100
Gly	Thr	Glu	Glu	Pro	Ala	Arg	Thr	Cys	Pro	Asn	Gly	Thr	Lys	Cys	Gln	
		275					280					285				

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CCC Pro 290	TAC Tyr	TGG Trp	GAA Glu	GGG Gly	CCC Pro	AAC Asn 295	AAC Asn	GGG Gly	ATC Ile	ACT Thr	CAG Gln 300	TTC Phe	GAC Asp	AAC Asn	ATC Ile	1148
CTG Leu 305	TTT Phe	GCA Ala	GTG Val	CTG Leu	ACT Thr 310	GTT Val	TTC Phe	CAG Gln	TGC Cys	ATA Ile 315	ACC Thr	ATG Met	GAA Glu	GGG Gly	TGG Trp 320	1196
ACT Thr	GAT Asp	CTC Leu	CTC Leu	TAC Tyr 325	AAT Asn	AGC Ser	AAC Asn	GAT Asp	GCC Ala 330	TCA Ser	GGG Gly	AAC Asn	ACT Thr	TGG Trp 335	AAC Asn	1244
TGG Trp	TTG Leu	TAC Tyr	TTC Phe 340	ATC Ile	CCC Pro	CTC Leu	ATC Ile	ATC Ile 345	GGC Gly	TCC Ser	TTT Phe 350	TTT Phe	ATG Met	CTG Leu	1292	
AAC Asn	CTT Leu	GTG Val 355	CTG Leu	GGT Gly	GTG Val	CTG Leu	TCA Ser 360	GGG Gly	GAG Glu	TTT Phe	GCC Ala 365	AAA Lys	GAA Glu	AGG Arg	GAA Glu	1340
CGG Arg 370	GTG Val	GAG Glu	AAC Asn	CGG Arg	CGG Arg	GCT Ala 375	TTT Phe	CTG Leu	AAG Lys	CTG Leu	AGG Arg 380	CGG Arg	CAA Gln	CAA Gln	CAG Gln	1388
ATT Ile 385	GAA Glu	CGT Arg	GAG Glu	CTC Leu	AAT Asn 390	GGG Gly	TAC Tyr	ATG Met	GAA Glu	TGG Trp 395	ATC Ile	TCA Ser	AAA Lys	GCA Ala	GAA Glu 400	1436
GAG Glu	GTG Val	ATC Ile	CTC Leu	GCC Ala 405	GAG Glu	GAT Asp	GAA Glu	ACT Thr	GAC Asp 410	GGG Gly	GAG Glu	CAG Gln	AGG Arg	CAT His 415	CCC Pro	1484
TTT Phe	GAT Asp	GGA Gly	GCT Ala 420	CTG Leu	CGG Arg	AGA Arg	ACC Thr	ACC Thr	ATA Ile	AAG Lys	AAA Lys	AGC Ser	AAG Lys	ACA Thr	GAT Asp	1532
TTG Leu	CTC Leu	AAC Asn 435	CCC Pro	GAA Glu	GAG Glu	GCT Ala	GAG Glu	GAT Asp	CAG Gln	CTG Leu	GCT Ala 445	GAT Asp	ATA Ile	GCC Ala	TCT Ser	1580
GTG Val 450	GGT Gly	TCT Ser	CCC Pro	TTC Phe	GCC Ala	CGA Arg 455	GCC Ala	AGC Ser	ATT Ile	AAA Lys	AGT Ser 460	GCC Ala	AAG Lys	CTG Leu	GAG Glu	1628
AAC Asn 465	TCG Ser	ACC Thr	TTT Phe	TTT Phe	CAC His 470	AAA Lys	AAG Lys	GAG Glu	AGG Arg	AGG Arg	ATG Met 475	CGT Arg	TTC Phe	TAC Tyr	ATC Ile 480	1676
CGC Arg	CGC Arg	ATG Met	GTC Val	AAA Lys 485	ACT Thr	CAG Gln	GCC Ala	TTC Phe	TAC Tyr	TGG Trp	ACT Thr	GTA Val	CTC Leu	AGT Ser	TTG Leu	1724
GTA Val	GCT Ala	CTC Leu	AAC Asn 500	ACG Thr	CTG Leu	TGT Cys	GTT Val	GCT Ala 505	ATT Ile	GTT Val	CAC His	TAC Tyr	AAC Asn 510	CAG Gln	CCC Pro	1772

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GAG	TGG	CTC	TCC	GAC	TTC	CTT	TAC	TAT	GCA	GAA	TTC	ATT	TTC	TTA	GGA	1820
Glu	Trp	Leu	Ser	Asp	Phe	Leu	Tyr	Tyr	Ala	Glu	Phe	Ile	Phe	Leu	Gly	
		515					520					525				
CTC	TTT	ATG	TCC	GAA	ATG	TTT	ATA	AAA	ATG	TAC	GGG	CTT	GGG	ACG	CGG	1868
Leu	Phe	Met	Ser	Glu	Met	Phe	Ile	Lys	Met	Tyr	Gly	Leu	Gly	Thr	Arg	
	530					535					540					
CCT	TAC	TTC	CAC	TCT	TCC	TTC	AAC	TGC	TTT	GAC	TGT	GGG	GTT	ATC	ATT	1916
Pro	Tyr	Phe	His	Ser	Ser	Phe	Asn	Cys	Phe	Asp	Cys	Gly	Val	Ile	Ile	
545					550					555					560	
GGG	AGC	ATC	TTC	GAG	GTC	ATC	TGG	GCT	GTC	ATA	AAA	CCT	GGC	ACA	TCC	1964
Gly	Ser	Ile	Phe	Glu	Val	Ile	Trp	Ala	Val	Ile	Lys	Pro	Gly	Thr	Ser	
				565					570					575		
TTT	GGA	ATC	AGC	GTG	TTA	CGA	GCC	CTC	AGG	TTA	TTG	CGT	ATT	TTC	AAA	2012
Phe	Gly	Ile	Ser	Val	Leu	Arg	Ala	Leu	Arg	Leu	Leu	Arg	Ile	Phe	Lys	
			580					585					590			
GTC	ACA	AAG	TAC	TGG	GCA	TCT	CTC	AGA	AAC	CTG	GTC	GTC	TCT	CTC	CTC	2060
Val	Thr	Lys	Tyr	Trp	Ala	Ser	Leu	Arg	Asn	Leu	Val	Val	Ser	Leu	Leu	
		595					600					605				
AAC	TCC	ATG	AAG	TCC	ATC	ATC	AGC	CTG	TTG	TTT	CTC	CTT	TTC	CTG	TTC	2108
Asn	Ser	Met	Lys	Ser	Ile	Ile	Ser	Leu	Leu	Phe	Leu	Leu	Phe	Leu	Phe	
	610					615					620					
ATT	GTC	GTC	TTC	GCC	CTT	TTG	GGA	ATG	CAA	CTC	TTC	GGC	GGC	CAG	TTT	2156
Ile	Val	Val	Phe	Ala	Leu	Leu	Gly	Met	Gln	Leu	Phe	Gly	Gly	Gln	Phe	
625					630					635					640	
AAT	TTC	GAT	GAA	GGG	ACT	CCT	CCC	ACC	AAC	TTC	GAT	ACT	TTT	CCA	GCA	2204
Asn	Phe	Asp	Glu	Gly	Thr	Pro	Pro	Thr	Asn	Phe	Asp	Thr	Phe	Pro	Ala	
			645						650					655		
GCA	ATA	ATG	ACG	GTG	TTT	CAG	ATC	CTG	ACG	GGC	GAA	GAC	TGG	AAC	GAG	2252
Ala	Ile	Met	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gly	Glu	Asp	Trp	Asn	Glu	
			660					665					670			
GTC	ATG	TAC	GAC	GGG	ATC	AAG	TCT	CAG	GGG	GGC	GTG	CAG	GGC	GGC	ATG	2300
Val	Met	Tyr	Asp	Gly	Ile	Lys	Ser	Gln	Gly	Gly	Val	Gln	Gly	Gly	Met	
		675					680					685				
GTG	TTC	TCC	ATC	TAT	TTC	ATT	GTA	CTG	ACG	CTC	TTT	GGG	AAC	TAC	ACC	2348
Val	Phe	Ser	Ile	Tyr	Phe	Ile	Val	Leu	Thr	Leu	Phe	Gly	Asn	Tyr	Thr	
	690					695					700					
CTC	CTG	AAT	GTG	TTC	TTG	GCC	ATC	GCT	GTG	GAC	AAT	CTG	GCC	AAC	GCC	2396
Leu	Leu	Asn	Val	Phe	Leu	Ala	Ile	Ala	Val	Asp	Asn	Leu	Ala	Asn	Ala	
705					710					715					720	
CAG	GAG	CTC	ACC	AAG	GTG	GAG	GCG	GAC	GAG	CAA	GAG	GAA	GAA	GAA	GCA	2444
Gln	Glu	Leu	Thr	Lys	Val	Glu	Ala	Asp	Glu	Gln	Glu	Glu	Glu	Glu	Ala	
				725					730					735		

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GCG	AAC	CAG	AAA	CTT	GCC	CTA	CAG	AAA	GCC	AAG	GAG	GTG	GCA	GAA	GTG	2492
Ala	Asn	Gln	Lys	Leu	Ala	Leu	Gln	Lys	Ala	Lys	Glu	Val	Ala	Glu	Val	
			740					745					750			
AGT	CCT	CTG	TCC	GCG	GCC	AAC	ATG	TCT	ATA	GCT	GTG	AAA	GAG	CAA	CAG	2540
Ser	Pro	Leu	Ser	Ala	Ala	Asn	Met	Ser	Ile	Ala	Val	Lys	Glu	Gln	Gln	
		755					760					765				
AAG	AAT	CAA	AAG	CCA	GCC	AAG	TCC	GTG	TGG	GAG	CAG	CGG	ACC	AGT	GAG	2588
Lys	Asn	Gln	Lys	Pro	Ala	Lys	Ser	Val	Trp	Glu	Gln	Arg	Thr	Ser	Glu	
	770					775					780					
ATG	CGA	AAG	CAG	AAC	TTG	CTG	GCC	AGC	CGG	GAG	GCC	CTG	TAT	AAC	GAA	2636
Met	Arg	Lys	Gln	Asn	Leu	Leu	Ala	Ser	Arg	Glu	Ala	Leu	Tyr	Asn	Glu	
785					790					795					800	
ATG	GAC	CCG	GAC	GAG	CGC	TGG	AAG	GCT	GCC	TAC	ACG	CGG	CAC	CTG	CGG	2684
Met	Asp	Pro	Asp	Glu	Arg	Trp	Lys	Ala	Ala	Tyr	Thr	Arg	His	Leu	Arg	
				805					810					815		
CCA	GAC	ATG	AAG	ACG	CAC	TTG	GAC	CGG	CCG	CTG	GTG	GTG	GAC	CCG	CAG	2732
Pro	Asp	Met	Lys	Thr	His	Leu	Asp	Arg	Pro	Leu	Val	Val	Asp	Pro	Gln	
			820					825					830			
GAG	AAC	CGC	AAC	AAC	AAC	ACC	AAC	AAG	AGC	CGG	GCG	GCC	GAG	CCC	ACC	2780
Glu	Asn	Arg	Asn	Asn	Asn	Thr	Asn	Lys	Ser	Arg	Ala	Ala	Glu	Pro	Thr	
		835					840					845				
GTG	GAC	CAG	CGC	CTC	GGC	CAG	CAG	CGC	GCC	GAG	GAC	TTC	CTC	AGG	AAA	2828
Val	Asp	Gln	Arg	Leu	Gly	Gln	Gln	Arg	Ala	Glu	Asp	Phe	Leu	Arg	Lys	
	850					855					860					
CAG	GCC	CGC	TAC	CAC	GAT	CGG	GCC	CGG	GAC	CCC	AGC	GGC	TCG	GCG	GGC	2876
Gln	Ala	Arg	Tyr	His	Asp	Arg	Ala	Arg	Asp	Pro	Ser	Gly	Ser	Ala	Gly	
865					870					875					880	
CTG	GAC	GCA	CGG	AGG	CCC	TGG	GCG	GGA	AGC	CAG	GAG	GCC	GAG	CTG	AGC	2924
Leu	Asp	Ala	Arg	Arg	Pro	Trp	Ala	Gly	Ser	Gln	Glu	Ala	Glu	Leu	Ser	
				885					890					895		
CGG	GAG	GGA	CCC	TAC	GGC	CGC	GAG	TCG	GAC	CAC	CAC	GCC	CGG	GAG	GGC	2972
Arg	Glu	Gly	Pro	Tyr	Gly	Arg	Glu	Ser	Asp	His	His	Ala	Arg	Glu	Gly	
			900					905					910			
AGC	CTG	GAG	CAA	CCC	GGG	TTC	TGG	GAG	GGC	GAG	GCC	GAG	CGA	GGC	AAG	3020
Ser	Leu	Glu	Gln	Pro	Gly	Phe	Trp	Glu	Gly	Glu	Ala	Glu	Arg	Gly	Lys	
		915					920					925				
GCC	GGG	GAC	CCC	CAC	CGG	AGG	CAC	GTG	CAC	CGG	CAG	GGG	GGC	AGC	AGG	3068
Ala	Gly	Asp	Pro	His	Arg	Arg	His	Val	His	Arg	Gln	Gly	Gly	Ser	Arg	
	930					935					940					
GAG	AGC	CGC	AGC	GGG	TCC	CCG	CGC	ACG	GGC	GCG	GAC	GGG	GAG	CAT	CGA	3116
Glu	Ser	Arg	Ser	Gly	Ser	Pro	Arg	Thr	Gly	Ala	Asp	Gly	Glu	His	Arg	
945					950				955						960	

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CGT	CAT	CGC	GCG	CAC	CGC	AGG	CCC	GGG	GAG	GAG	GGT	CCG	GAG	GAC	AAG	3164
Arg	His	Arg	Ala	His	Arg	Arg	Pro	Gly	Glu	Glu	Gly	Pro	Glu	Asp	Lys	
				965					970					975		
GCG	GAG	CGG	AGG	GCG	CGG	CAC	CGC	GAG	GGC	AGC	CGG	CCG	GCC	CGG	GGC	3212
Ala	Glu	Arg	Arg	Ala	Arg	His	Arg	Glu	Gly	Ser	Arg	Pro	Ala	Arg	Gly	
			980					985					990			
GGC	GAG	GGC	GAG	GGC	GAG	GGC	CCC	GAC	GGG	GGC	GAG	CGC	AGG	AGA	AGG	3260
Gly	Glu	Gly	Glu	Gly	Glu	Gly	Pro	Asp	Gly	Gly	Glu	Arg	Arg	Arg	Arg	
		995					1000					1005				
CAC	CGG	CAT	GGC	GCT	CCA	GCC	ACG	TAC	GAG	GGG	GAC	GCG	CGG	AGG	GAG	3308
His	Arg	His	Gly	Ala	Pro	Ala	Thr	Tyr	Glu	Gly	Asp	Ala	Arg	Arg	Glu	
	1010					1015					1020					
GAC	AAG	GAG	CGG	AGG	CAT	CGG	AGG	AGG	AAA	GAG	AAC	CAG	GGC	TCC	GGG	3356
Asp	Lys	Glu	Arg	Arg	His	Arg	Arg	Arg	Lys	Glu	Asn	Gln	Gly	Ser	Gly	
1025					1030					1035					1040	
GTC	CCT	GTG	TCG	GGC	CCC	AAC	CTG	TCA	ACC	ACC	CGG	CCA	ATC	CAG	CAG	3404
Val	Pro	Val	Ser	Gly	Pro	Asn	Leu	Ser	Thr	Thr	Arg	Pro	Ile	Gln	Gln	
				1045					1050					1055		
GAC	CTG	GGC	CGC	CAA	GAC	CCA	CCC	CTG	GCA	GAG	GAT	ATT	GAC	AAC	ATG	3452
Asp	Leu	Gly	Arg	Gln	Asp	Pro	Pro	Leu	Ala	Glu	Asp	Ile	Asp	Asn	Met	
			1060					1065					1070			
AAG	AAC	AAC	AAG	CTG	GCC	ACC	GCG	GAG	TCG	GCC	GCT	CCC	CAC	GGC	AGC	3500
Lys	Asn	Asn	Lys	Leu	Ala	Thr	Ala	Glu	Ser	Ala	Ala	Pro	His	Gly	Ser	
		1075					1080					1085				
CTT	GGC	CAC	GCC	GGC	CTG	CCC	CAG	AGC	CCA	GCC	AAG	ATG	GGA	AAC	AGC	3548
Leu	Gly	His	Ala	Gly	Leu	Pro	Gln	Ser	Pro	Ala	Lys	Met	Gly	Asn	Ser	
	1090					1095					1100					
ACC	GAC	CCC	GGC	CCC	ATG	CTG	GCC	ATC	CCT	GCC	ATG	GCC	ACC	AAC	CCC	3596
Thr	Asp	Pro	Gly	Pro	Met	Leu	Ala	Ile	Pro	Ala	Met	Ala	Thr	Asn	Pro	
1105					1110					1115					1120	
CAG	AAC	GCC	GCC	AGC	CGC	CGG	ACG	CCC	AAC	AAC	CCG	GGG	AAC	CCA	TCC	3644
Gln	Asn	Ala	Ala	Ser	Arg	Arg	Thr	Pro	Asn	Asn	Pro	Gly	Asn	Pro	Ser	
				1125					1130					1135		
AAT	CCC	GGC	CCC	CCC	AAG	ACC	CCC	GAG	AAT	AGC	CTT	ATC	GTC	ACC	AAC	3692
Asn	Pro	Gly	Pro	Pro	Lys	Thr	Pro	Glu	Asn	Ser	Leu	Ile	Val	Thr	Asn	
			1140					1145					1150			
CCC	AGC	GGC	ACC	CAG	ACC	AAT	TCA	GCT	AAG	ACT	GCC	AGG	AAA	CCC	GAC	3740
Pro	Ser	Gly	Thr	Gln	Thr	Asn	Ser	Ala	Lys	Thr	Ala	Arg	Lys	Pro	Asp	
		1155					1160					1165				
CAC	ACC	ACA	GTG	GAC	ATC	CCC	CCA	GCC	TGC	CCA	CCC	CCC	CTC	AAC	CAC	3788
His	Thr	Thr	Val	Asp	Ile	Pro	Pro	Ala	Cys	Pro	Pro	Pro	Leu	Asn	His	
	1170					1175					1180					

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ACC	GTC	GTA	CAA	GTG	AAC	AAA	AAC	GCC	AAC	CCA	GAC	CCA	CTG	CCA	AAA	3836
Thr	Val	Val	Gln	Val	Asn	Lys	Asn	Ala	Asn	Pro	Asp	Pro	Leu	Pro	Lys	
1185					1190					1195					1200	
AAA	GAG	GAA	GAG	AAG	AAG	GAG	GAG	GAG	GAA	GAC	GAC	CGT	GGG	GAA	GAC	3884
Lys	Glu	Glu	Glu	Lys	Lys	Glu	Glu	Glu	Glu	Asp	Asp	Arg	Gly	Glu	Asp	
				1205					1210					1215		
GGC	CCT	AAG	CCA	ATG	CCT	CCC	TAT	AGC	TCC	ATG	TTC	ATC	CTG	TCC	ACG	3932
Gly	Pro	Lys	Pro	Met	Pro	Pro	Tyr	Ser	Ser	Met	Phe	Ile	Leu	Ser	Thr	
			1220					1225					1230			
ACC	AAC	CCC	CTT	CGC	CGC	CTG	TGC	CAT	TAC	ATC	CTG	AAC	CTG	CGC	TAC	3980
Thr	Asn	Pro	Leu	Arg	Arg	Leu	Cys	His	Tyr	Ile	Leu	Asn	Leu	Arg	Tyr	
		1235					1240					1245				
TTT	GAG	ATG	TGC	ATC	CTC	ATG	GTC	ATT	GCC	ATG	AGC	AGC	ATC	GCC	CTG	4028
Phe	Glu	Met	Cys	Ile	Leu	Met	Val	Ile	Ala	Met	Ser	Ser	Ile	Ala	Leu	
1250						1255					1260					
GCC	GCC	GAG	GAC	CCT	GTG	CAG	CCC	AAC	GCA	CCT	CGG	AAC	AAC	GTG	CTG	4076
Ala	Ala	Glu	Asp	Pro	Val	Gln	Pro	Asn	Ala	Pro	Arg	Asn	Asn	Val	Leu	
1265					1270					1275					1280	
CGA	TAC	TTT	GAC	TAC	GTT	TTT	ACA	GGC	GTC	TTC	ACC	TTT	GAG	ATG	GTG	4124
Arg	Tyr	Phe	Asp	Tyr	Val	Phe	Thr	Gly	Val	Phe	Thr	Phe	Glu	Met	Val	
			1285						1290					1295		
ATC	AAG	ATG	ATT	GAC	CTG	GGG	CTC	GTC	CTG	CAT	CAG	GGT	GCC	TAC	TTC	4172
Ile	Lys	Met	Ile	Asp	Leu	Gly	Leu	Val	Leu	His	Gln	Gly	Ala	Tyr	Phe	
			1300					1305					1310			
CGT	GAC	CTC	TGG	AAT	ATT	CTC	GAC	TTC	ATA	GTG	GTC	AGT	GGG	GCC	CTG	4220
Arg	Asp	Leu	Trp	Asn	Ile	Leu	Asp	Phe	Ile	Val	Val		Ser	Gly	Ala	
		1315					1320					1325				
GTA	GCC	TTT	GCC	TTC	ACT	GGC	AAT	AGC	AAA	GGA	AAA	GAC	ATC	AAC	ACG	4268
Val	Ala	Phe	Ala	Phe	Thr	Gly	Asn	Ser	Lys	Gly	Lys	Asp	Ile	Asn	Thr	
1330						1335					1340					
ATT	AAA	TCC	CTC	CGA	GTC	CTC	CGG	GTG	CTA	CGA	CCT	CTT	AAA	ACC	ATC	4316
Ile	Lys	Ser	Leu	Arg	Val	Leu	Arg	Val	Leu	Arg	Pro	Leu	Lys	Thr	Ile	
1345					1350					1355					1360	
AAG	CGG	CTG	CCA	AAG	CTC	AAG	GCT	GTG	TTT	GAC	TGT	GTG	GTG	AAC	TCA	4364
Lys	Arg	Leu	Pro	Lys	Leu	Lys	Ala	Val	Phe	Asp	Cys	Val	Val	Asn	Ser	
				1365					1370					1375		
CTT	AAA	AAC	GTC	TTC	AAC	ATC	CTC	ATC	GTC	TAC	ATG	CTA	TTC	ATG	TTC	4412
Leu	Lys	Asn	Val	Phe	Asn	Ile	Leu	Ile	Val	Tyr	Met	Leu	Phe	Met	Phe	
			1380					1385					1390			
ATC	TTC	GCC	GTG	GTG	GCT	GTG	CAG	CTC	TTC	AAG	GGG	AAA	TTC	TTC	CAC	4460
Ile	Phe	Ala	Val	Val	Ala	Val	Gln	Leu	Phe	Lys	Gly	Lys	Phe	Phe	His	
		1395					1400					1405				

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TGC ACT GAC GAG TCC AAA GAG TTT GAG AAA GAT TGT CGA GGC AAA TAC Cys Thr Asp Glu Ser Lys Glu Phe Glu Lys Asp Cys Arg Gly Lys Tyr 1410 1415 1420	4508
CTC CTC TAC GAG AAG AAT GAG GTG AAG GCG CGA GAC CGG GAG TGG AAG Leu Leu Tyr Glu Lys Asn Glu Val Lys Ala Arg Asp Arg Glu Trp Lys 1425 1430 1435 1440	4556
AAG TAT GAA TTC CAT TAC GAC AAT GTG CTG TGG GCT CTG CTG ACC CTC Lys Tyr Glu Phe His Tyr Asp Asn Val Leu Trp Ala Leu Leu Thr Leu 1445 1450 1455	4604
TTC ACC GTG TCC ACG GGA GAA GGC TGG CCA CAG GTC CTC AAG CAT TCG Phe Thr Val Ser Thr Gly Glu Gly Trp Pro Gln Val Leu Lys His Ser 1460 1465 1470	4652
GTG GAC GCC ACC TTT GAG AAC CAG GGC CCC AGC CCC GGG TAC CGC ATG Val Asp Ala Thr Phe Glu Asn Gln Gly Pro Ser Pro Gly Tyr Arg Met 1475 1480 1485	4700
GAG ATG TCC ATT TTC TAC GTC GTC TAC TTT GTG GTG TTC CCC TTC TTC Glu Met Ser Ile Phe Tyr Val Val Tyr Phe Val Val Phe Pro Phe Phe 1490 1495 1500	4748
TTT GTC AAT ATC TTT GTG GCC TTG ATC ATC ATC ACC TTC CAG GAG CAA Phe Val Asn Ile Phe Val Ala Leu Ile Ile Ile Thr Phe Gln Glu Gln 1505 1510 1515 1520	4796
GGG GAC AAG ATG ATG GAG GAA TAC AGC CTG GAG AAA AAT GAG AGG GCC Gly Asp Lys Met Met Glu Glu Tyr Ser Leu Glu Lys Asn Glu Arg Ala 1525 1530 1535	4844
TGC ATT GAT TTC GCC ATC AGC GCC AAG CCG CTG ACC CGA CAC ATG CCG Cys Ile Asp Phe Ala Ile Ser Ala Lys Pro Leu Thr Arg His Met Pro 1540 1545 1550	4892
CAG AAC AAG CAG AGC TTC CAG TAC CGC ATG TGG CAG TTC GTG GTG TCT Gln Asn Lys Gln Ser Phe Gln Tyr Arg Met Trp Gln Phe Val Val Ser 1555 1560 1565	4940
CCG CCT TTC GAG TAC ACG ATC ATG GCC ATG ATC GCC CTC AAC ACC ATC Pro Pro Phe Glu Tyr Thr Ile Met Ala Met Ile Ala Leu Asn Thr Ile 1570 1575 1580	4988
GTG CTT ATG ATG AAG TTC TAT GGG GCT TCT GTT GCT TAT GAA AAT GCC Val Leu Met Met Lys Phe Tyr Gly Ala Ser Val Ala Tyr Glu Asn Ala 1585 1590 1595 1600	5036
CTG CGG GTG TTC AAC ATC GTC TTC ACC TCC CTC TTC TCT CTG GAA TGT Leu Arg Val Phe Asn Ile Val Phe Thr Ser Leu Phe Ser Leu Glu Cys 1605 1610 1615	5084
GTG CTG AAA GTC ATG GCT TTT GGG ATT CTG AAT TAT TTC CGC GAT GCC Val Leu Lys Val Met Ala Phe Gly Ile Leu Asn Tyr Phe Arg Asp Ala 1620 1625 1630	5132

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TGG AAC ATC TTC GAC TTT GTG ACT GTT CTG GGC AGC ATC ACC GAT ATC	5180
Trp Asn Ile Phe Asp Phe Val Thr Val Leu Gly Ser Ile Thr Asp Ile	
1635 1640 1645	
CTC GTG ACT GAG TTT GGG AAT CCG AAT AAC TTC ATC AAC CTG AGC TTT	5228
Leu Val Thr Glu Phe Gly Asn Pro Asn Asn Phe Ile Asn Leu Ser Phe	
1650 1655 1660	
CTC CGC CTC TTC CGA GCT GCC CGG CTC ATC AAA CTT CTC CGT CAG GGT	5276
Leu Arg Leu Phe Arg Ala Ala Arg Leu Ile Lys Leu Leu Arg Gln Gly	
1665 1670 1675 1680	
TAC ACC ATC CGC ATT CTT CTC TGG ACC TTT GTG CAG TCC TTC AAG GCC	5324
Tyr Thr Ile Arg Ile Leu Leu Trp Thr Phe Val Gln Ser Phe Lys Ala	
1685 1690 1695	
CTG CCT TAT GTC TGT CTG CTG ATC GCC ATG CTC TTC TTC ATC TAT GCC	5372
Leu Pro Tyr Val Cys Leu Leu Ile Ala Met Leu Phe Phe Ile Tyr Ala	
1700 1705 1710	
ATC ATT GGG ATG CAG GTG TTT GGT AAC ATT GGC ATC GAC GTG GAG GAC	5420
Ile Ile Gly Met Gln Val Phe Gly Asn Ile Gly Ile Asp Val Glu Asp	
1715 1720 1725	
GAG GAC AGT GAT GAA GAT GAG TTC CAA ATC ACT GAG CAC AAT AAC TTC	5468
Glu Asp Ser Asp Glu Asp Glu Phe Gln Ile Thr Glu His Asn Asn Phe	
1730 1735 1740	
CGG ACC TTC TTC CAG GCC CTC ATG CTT CTC TTC CGG AGT GCC ACC GGG	5516
Arg Thr Phe Phe Gln Ala Leu Met Leu Leu Phe Arg Ser Ala Thr Gly	
1745 1750 1755 1760	
GAA GCT TGG CAC AAC ATC ATG CTT TCC TGC CTC AGC GGG AAA CCG TGT	5564
Glu Ala Trp His Asn Ile Met Leu Ser Cys Leu Ser Gly Lys Pro Cys	
1765 1770 1775	
GAT AAG AAC TCT GGC ATC CTG ACT CGA GAG TGT GGC AAT GAA TTT GCT	5612
Asp Lys Asn Ser Gly Ile Leu Thr Arg Glu Cys Gly Asn Glu Phe Ala	
1780 1785 1790	
TAT TTT TAC TTT GTT TCC TTC ATC TTC CTC TGC TCG TTT CTG ATG CTG	5660
Tyr Phe Tyr Phe Val Ser Phe Ile Phe Leu Cys Ser Phe Leu Met Leu	
1795 1800 1805	
AAT CTC TTT GTC GCC GTC ATC ATG GAC AAC TTT GAG TAC CTC ACC CGA	5708
Asn Leu Phe Val Ala Val Ile Met Asp Asn Phe Glu Tyr Leu Thr Arg	
1810 1815 1820	
GAC TCC TCC ATC CTG GGC CCC CAC CAC CTG GAT GAG TAC GTG CGT GTC	5756
Asp Ser Ser Ile Leu Gly Pro His His Leu Asp Glu Tyr Val Arg Val	
1825 1830 1835 1840	
TGG GCC GAG TAT GAC CCC GCA GCT TGG GGC CGC ATG CCT TAC CTG GAC	5804
Trp Ala Glu Tyr Asp Pro Ala Ala Trp Gly Arg Met Pro Tyr Leu Asp	
1845 1850 1855	

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ATG	TAT	CAG	ATG	CTG	AGA	CAC	ATG	TCT	CCG	CCC	CTG	GGT	CTG	GGG	AAG	5852
Met	Tyr	Gln	Met	Leu	Arg	His	Met	Ser	Pro	Pro	Leu	Gly	Leu	Gly	Lys	
			1860					1865					1870			
AAG	TGT	CCG	GCC	AGA	GTG	GCT	TAC	AAG	CGG	CTT	CTG	CGG	ATG	GAC	CTG	5900
Lys	Cys	Pro	Ala	Arg	Val	Ala	Tyr	Lys	Arg	Leu	Leu	Arg	Met	Asp	Leu	
		1875					1880					1885				
CCC	GTC	GCA	GAT	GAC	AAC	ACC	GTC	CAC	TTC	AAT	TCC	ACC	CTC	ATG	GCT	5948
Pro	Val	Ala	Asp	Asp	Asn	Thr	Val	His	Phe	Asn	Ser	Thr	Leu	Met	Ala	
	1890					1895					1900					
CTG	ATC	CGC	ACA	GCC	CTG	GAC	ATC	AAG	ATT	GCC	AAG	GGA	GGA	GCC	GAC	5996
Leu	Ile	Arg	Thr	Ala	Leu	Asp	Ile	Lys	Ile	Ala	Lys	Gly	Gly	Ala	Asp	
1905					1910					1915					1920	
AAA	CAG	CAG	ATG	GAC	GCT	GAG	CTG	CGG	AAG	GAG	ATG	ATG	GCG	ATT	TGG	6044
Lys	Gln	Gln	Met	Asp	Ala	Glu	Leu	Arg	Lys	Glu	Met	Met	Ala	Ile	Trp	
				1925					1930					1935		
CCC	AAT	CTG	TCC	CAG	AAG	ACG	CTA	GAC	CTG	CTG	GTC	ACA	CCT	CAC	AAG	6092
Pro	Asn	Leu	Ser	Gln	Lys	Thr	Leu	Asp	Leu	Leu	Val	Thr	Pro	His	Lys	
			1940					1945					1950			
TCC	ACG	GAC	CTC	ACC	GTG	GGG	AAG	ATC	TAC	GCA	GCC	ATG	ATG	ATC	ATG	6140
Ser	Thr	Asp	Leu	Thr	Val	Gly	Lys	Ile	Tyr	Ala	Ala	Met	Met	Ile	Met	
		1955				1960						1965				
GAG	TAC	TAC	CGG	CAG	AGC	AAG	GCC	AAG	AAG	CTG	CAG	GCC	ATG	CGC	GAG	6188
Glu	Tyr	Tyr	Arg	Gln	Ser	Lys	Ala	Lys	Lys	Leu	Gln	Ala	Met	Arg	Glu	
	1970					1975					1980					
GAG	CAG	GAC	CGG	ACA	CCC	CTC	ATG	TTC	CAG	CGC	ATG	GAG	CCC	CCG	TCC	6236
Glu	Gln	Asp	Arg	Thr	Pro	Leu	Met	Phe	Gln	Arg	Met	Glu	Pro	Pro	Ser	
1985					1990					1995					2000	
CCA	ACG	CAG	GAA	GGG	GGA	CCT	GGC	CAG	AAC	GCC	CTC	CCC	TCC	ACC	CAG	6284
Pro	Thr	Gln	Glu	Gly	Gly	Pro	Gly	Gln	Asn	Ala	Leu	Pro	Ser	Thr	Gln	
				2005					2010					2015		
CTG	GAC	CCA	GGA	GGA	GCC	CTG	ATG	GCT	CAC	GAA	AGC	GGC	CTC	AAG	GAG	6332
Leu	Asp	Pro	Gly	Gly	Ala	Leu	Met	Ala	His	Glu	Ser	Gly	Leu	Lys	Glu	
			2020					2025					2030			
AGC	CCG	TCC	TGG	GTG	ACC	CAG	CGT	GCC	CAG	GAG	ATG	TTC	CAG	AAG	ACG	6380
Ser	Pro	Ser	Trp	Val	Thr	Gln	Arg	Ala	Gln	Glu	Met	Phe	Gln	Lys	Thr	
		2035					2040					2045				
GGC	ACA	TGG	AGT	CCG	GAA	CAA	GGC	CCC	CCT	ACC	GAC	ATG	CCC	AAC	AGC	6428
Gly	Thr	Trp	Ser	Pro	Glu	Gln	Gly	Pro	Pro	Thr	Asp	Met	Pro	Asn	Ser	
	2050					2055					2060					
CAG	CCT	AAC	TCT	CAG	TCC	GTG	GAG	ATG	CGA	GAG	ATG	GGC	AGA	GAT	GGC	6476
Gln	Pro	Asn	Ser	Gln	Ser	Val	Glu	Met	Arg	Glu	Met	Gly	Arg	Asp	Gly	
2065					2070					2075					2080	

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TAC TCC GAC AGC GAG CAC TAC CTC CCC ATG GAA GGC CAG GGC CGG GCT	6524
Tyr Ser Asp Ser Glu His Tyr Leu Pro Met Glu Gly Gln Gly Arg Ala	
2085 2090 2095	
GCC TCC ATG CCC CGC CTC CCT GCA GAG AAC CAG AGG AGA AGG GGC CGG	6572
Ala Ser Met Pro Arg Leu Pro Ala Glu Asn Gln Arg Arg Arg Gly Arg	
2100 2105 2110	
CCA CGT GGG AAT AAC CTC AGT ACC ATC TCA GAC ACC AGC CCC ATG AAG	6620
Pro Arg Gly Asn Asn Leu Ser Thr Ile Ser Asp Thr Ser Pro Met Lys	
2115 2120 2125	
CGT TCA GCC TCC GTG CTG GGC CCC AAG GCC CGA CGC CTG GAC GAT TAC	6668
Arg Ser Ala Ser Val Leu Gly Pro Lys Ala Arg Arg Leu Asp Asp Tyr	
2130 2135 2140	
TCG CTG GAG CGG GTC CCG CCC GAG GAG AAC CAG CGG CAC CAC CAG CGG	6716
Ser Leu Glu Arg Val Pro Pro Glu Glu Asn Gln Arg His His Gln Arg	
2145 2150 2155 2160	
CGC CGC GAC CGC AGC CAC CGC GCC TCT GAG CGC TCC CTG GGC CGC TAC	6764
Arg Arg Asp Arg Ser His Arg Ala Ser Glu Arg Ser Leu Gly Arg Tyr	
2165 2170 2175	
ACC GAT GTG GAC ACA GGC TTG GGG ACA GAC CTG AGC ATG ACC ACC CAA	6812
Thr Asp Val Asp Thr Gly Leu Gly Thr Asp Leu Ser Met Thr Thr Gln	
2180 2185 2190	
TCC GGG GAC CTG CCG TCG AAG GAG CGG GAC CAG GAG CGG GGC CGG CCC	6860
Ser Gly Asp Leu Pro Ser Lys Glu Arg Asp Gln Glu Arg Gly Arg Pro	
2195 2200 2205	
AAG GAT CGG AAG CAT CGA CAG CAC CAC CAC CAC CAC CAC CAC CAC	6908
Lys Asp Arg Lys His Arg Gln His His His His His His His His	
2210 2215 2220	
CAT CCC CCG CCC CCC GAC AAG GAC CGC TAT GCC CAG GAA CGG CCG GAC	6956
His Pro Pro Pro Pro Asp Lys Asp Arg Tyr Ala Gln Glu Arg Pro Asp	
2225 2230 2235 2240	
CAC GGC CGG GCA CGG GCT CGG GAC CAG CGC TGG TCC CGC TCG CCC AGC	7004
His Gly Arg Ala Arg Ala Arg Asp Gln Arg Trp Ser Arg Ser Pro Ser	
2245 2250 2255	
GAG GGC CGA GAG CAC ATG GCG CAC CGG CAG TAGTTCCGTA AGTGGAAGCC	7054
Glu Gly Arg Glu His Met Ala His Arg Gln	
2260 2265	
CAGCCCCCTC AACATCTGGT ACCAGCACTC CGCGGCGGGG CCGCCGCCAG CTCCCCCAGA	7114
CCCCCTCCAC CCCCCGGCCA CACGTGTCCT ATTCCCCCTGT GATCCGTAAG GCCGGCGGCT	7174
CGGGGCCCCC GCAGCAGCAG CAGCAGCAGC AGGCGGTGGC CAGGCCGGGC CGGGCGGCCA	7234
CCAGCGGCCC TCGGAGGTAC CCAGGCCCCA CGGCCGAGCC TCTGGCCGGA GATCGGCCGC	7294

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CCACGGGGGG CCACAGCAGC GGCCGCTCGC CCAGGATGGA GAGGCGGGTC CCAGGCCCGG 7354
CCCGGAGCGA GTCCCCCAGG GCCTGTCGAC ACGGCGGGGC CCGGTGGCCG GCATCTGGCC 7414
CGCACGTGTC CGAGGGGGCCC CCGGGTCCCC GGCACCATGG CTACTACCGG GGCTCCGACT 7474
ACGACGAGGC CGATGGCCCC GGCAGCGGGG GCGGCGAGGA GGCCATGGCC GGGGCCTACG 7534
ACGCGCCACC CCCCCTACGA CACGCGTCTT CGGGCGCCAC CGGGCGCTCG CCCAGGACTC 7594
CCCGGGCCTC GGGCCCGGCC TGCGCCTCGC CTTCTCGGCA CGGCCGGCGA CTCCCCAACG 7654
GCTACTACCC GCGGCACGGA CTGGCCAGGC CCCGCGGGCC GGGCTCCAGG AAGGGCCTGC 7714
ACGAACCTTA CAGCGAGAGT GACGATGATT GGTGCTAAGC CCGGCGGAGG TGGCGCCCGC 7774
CCGGCCCCCCC ACGCACC 7791

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(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7032 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 166..6921
- (D) OTHER INFORMATION: /standard_name= "Alpha-1E-1"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

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GCTGCTGCTG CCTCTCCGAA GAGCTCGCGG AGCTCCCCAG AGGCGGTGGT CCCCCTGCTT 60
GTCTGGATGC GGCTCTGAGT CTCCGTGTGT CTTTCTGCTT GTTGCTGTGT GCGGGTGTTC 120
GGCCGCGATC ACCTTTGTGT GTCTTCTGTC TGTTTAAACC TCAGG ATG GCT CGC 174
                               Met Ala Arg
                               1
TTC GGG GAG GCG GTG GTC GCC AGG CCA GGG TCC GGC GAT GGA GAC TCG 222
Phe Gly Glu Ala Val Val Ala Arg Pro Gly Ser Gly Asp Gly Asp Ser
      5                               10                               15
GAC CAG AGC AGG AAC CGG CAA GGA ACC CCC GTG CCG GCC TCG GGG CAG 270
Asp Gln Ser Arg Asn Arg Gln Gly Thr Pro Val Pro Ala Ser Gly Gln
      20                               25                               30                               35
GCG GCC GCC TAC AAG CAG ACG AAA GCA CAG AGG GCG CGG ACT ATG GCT 318
Ala Ala Ala Tyr Lys Gln Thr Lys Ala Gln Arg Ala Arg Thr Met Ala
      40                               45                               50

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TTG	TAC	AAC	CCC	ATT	CCC	GTC	CGG	CAG	AAC	TGT	TTC	ACC	GTC	AAC	AGA	366
Leu	Tyr	Asn	Pro	Ile	Pro	Val	Arg	Gln	Asn	Cys	Phe	Thr	Val	Asn	Arg	
		55						60					65			
TCC	CTG	TTC	ATC	TTC	GGA	GAA	GAT	AAC	ATT	GTC	AGG	AAA	TAT	GCC	AAG	414
Ser	Leu	Phe	Ile	Phe	Gly	Glu	Asp	Asn	Ile	Val	Arg	Lys	Tyr	Ala	Lys	
		70					75					80				
AAG	CTC	ATC	GAT	TGG	CCG	CCA	TTT	GAG	TAC	ATG	ATC	CTG	GCC	ACC	ATC	462
Lys	Leu	Ile	Asp	Trp	Pro	Pro	Phe	Glu	Tyr	Met	Ile	Leu	Ala	Thr	Ile	
	85					90					95					
ATT	GCC	AAC	TGC	ATC	GTC	CTG	GCC	CTG	GAG	CAG	CAT	CTT	CCT	GAG	GAT	510
Ile	Ala	Asn	Cys	Ile	Val	Leu	Ala	Leu	Glu	Gln	His	Leu	Pro	Glu	Asp	
100					105					110					115	
GAC	AAG	ACC	CCC	ATG	TCC	CGA	AGA	CTG	GAG	AAG	ACA	GAA	CCT	TAT	TTC	558
Asp	Lys	Thr	Pro	Met	Ser	Arg	Arg	Leu	Glu	Lys	Thr	Glu	Pro	Tyr	Phe	
				120					125					130		
ATT	GGG	ATC	TTT	TGC	TTT	GAA	GCT	GGG	ATC	AAA	ATT	GTG	GCC	CTG	GGG	606
Ile	Gly	Ile	Phe	Cys	Phe	Glu	Ala	Gly	Ile	Lys	Ile	Val	Ala	Leu	Gly	
			135					140					145			
TTC	ATC	TTC	CAT	AAG	GGC	TCT	TAC	CTC	CGC	AAT	GGC	TGG	AAT	GTC	ATG	654
Phe	Ile	Phe	His	Lys	Gly	Ser	Tyr	Leu	Arg	Asn	Gly	Trp	Asn	Val	Met	
		150					155					160				
GAC	TTC	ATC	GTG	GTC	CTC	AGT	GGC	ATC	CTG	GCC	ACT	GCA	GGA	ACC	CAC	702
Asp	Phe	Ile	Val	Val	Leu	Ser	Gly	Ile	Leu	Ala	Thr	Ala	Gly	Thr	His	
	165					170					175					
TTC	AAT	ACT	CAC	GTG	GAC	CTG	AGG	ACC	CTC	CGG	GCT	GTG	CGT	GTC	CTG	750
Phe	Asn	Thr	His	Val	Asp	Leu	Arg	Thr	Leu	Arg	Ala	Val	Arg	Val	Leu	
180					185					190					195	
CGG	CCT	TTG	AAG	CTC	GTG	TCA	GGG	ATA	CCT	AGC	CTG	CAG	ATT	GTG	TTG	798
Arg	Pro	Leu	Lys	Leu	Val	Ser	Gly	Ile	Pro	Ser	Leu	Gln	Ile	Val	Leu	
				200					205					210		
AAG	TCC	ATC	ATG	AAG	GCC	ATG	GTA	CCT	CTT	CTG	CAG	ATT	GGC	CTT	CTG	846
Lys	Ser	Ile	Met	Lys	Ala	Met	Val	Pro	Leu	Leu	Gln	Ile	Gly	Leu	Leu	
			215					220					225			
CTC	TTC	TTT	GCC	ATC	CTG	ATG	TTT	GCT	ATC	ATT	GGT	TTG	GAG	TTC	TAC	894
Leu	Phe	Phe	Ala	Ile	Leu	Met	Phe	Ala	Ile	Ile	Gly	Leu	Glu	Phe	Tyr	
		230					235					240				
AGT	GGC	AAG	TTA	CAT	CGA	GCG	TGC	TTC	ATG	AAC	AAT	TCA	GGT	ATT	CTA	942
Ser	Gly	Lys	Leu	His	Arg	Ala	Cys	Phe	Met	Asn	Asn	Ser	Gly	Ile	Leu	
	245					250					255					
GAA	GGA	TTT	GAC	CCC	CCT	CAC	CCA	TGT	GGT	GTG	CAG	GGC	TGC	CCA	GCT	990
Glu	Gly	Phe	Asp	Pro	Pro	His	Pro	Cys	Gly	Val	Gln	Gly	Cys	Pro	Ala	
260					265					270					275	

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GGT	TAT	GAA	TGC	AAG	GAC	TGG	ATC	GGC	CCC	AAT	GAT	GGG	ATC	ACC	CAG	1038
Gly	Tyr	Glu	Cys	Lys	Asp	Trp	Ile	Gly	Pro	Asn	Asp	Gly	Ile	Thr	Gln	
				280					285					290		
TTT	GAT	AAC	ATC	CTT	TTT	GCT	GTG	CTG	ACT	GTC	TTC	CAG	TGC	ATC	ACC	1086
Phe	Asp	Asn	Ile	Leu	Phe	Ala	Val	Leu	Thr	Val	Phe	Gln	Cys	Ile	Thr	
			295					300					305			
ATG	GAA	GGG	TGG	ACC	ACT	GTG	CTG	TAC	AAT	ACC	AAT	GAT	GCC	TTA	GGA	1134
Met	Glu	Gly	Trp	Thr	Thr	Val	Leu	Tyr	Asn	Thr	Asn	Asp	Ala	Leu	Gly	
		310					315					320				
GCC	ACC	TGG	AAT	TGG	CTG	TAC	TTC	ATC	CCC	CTC	ATC	ATC	ATT	GGA	TCC	1182
Ala	Thr	Trp	Asn	Trp	Leu	Tyr	Phe	Ile	Pro	Leu	Ile	Ile	Ile	Gly	Ser	
	325					330					335					
TTC	TTT	GTT	CTC	AAC	CTA	GTC	CTG	GGA	GTG	CTT	TCC	GGG	GAA	TTT	GCC	1230
Phe	Phe	Val	Leu	Asn	Leu	Val	Leu	Gly	Val	Leu	Ser	Gly	Glu	Phe	Ala	
340					345					350					355	
AAA	GAG	AGA	GAG	AGA	GTG	GAG	AAC	CGA	AGG	GCT	TTC	ATG	AAG	CTG	CGG	1278
Lys	Glu	Arg	Glu	Arg	Val	Glu	Asn	Arg	Arg	Ala	Phe	Met	Lys	Leu	Arg	
				360					365					370		
CGC	CAG	CAG	CAG	ATT	GAG	CGT	GAG	CTG	AAT	GGC	TAC	CGT	GCC	TGG	ATA	1326
Arg	Gln	Gln	Gln	Ile	Glu	Arg	Glu	Leu	Asn	Gly	Tyr	Arg	Ala	Trp	Ile	
			375					380					385			
GAC	AAA	GCA	GAG	GAA	GTC	ATG	CTC	GCT	GAA	GAA	AAT	AAA	AAT	GCT	GGA	1374
Asp	Lys	Ala	Glu	Glu	Val	Met	Leu	Ala	Glu	Glu	Asn	Lys	Asn	Ala	Gly	
	390						395					400				
ACA	TCC	GCC	TTA	GAA	GTG	CTT	CGA	AGG	GCA	ACC	ATC	AAG	AGG	AGC	CGG	1422
Thr	Ser	Ala	Leu	Glu	Val	Leu	Arg	Arg	Ala	Thr	Ile	Lys	Arg	Ser	Arg	
	405					410					415					
ACA	GAG	GCC	ATG	ACT	CGA	GAC	TCC	AGT	GAT	GAG	CAC	TGT	GTT	GAT	ATC	1470
Thr	Glu	Ala	Met	Thr	Arg	Asp	Ser	Ser	Asp	Glu	His	Cys	Val	Asp	Ile	
420					425					430					435	
TCC	TCT	GTG	GGC	ACA	CCT	CTG	GCC	CGA	GCC	AGT	ATC	AAA	AGT	GCA	AAG	1518
Ser	Ser	Val	Gly	Thr	Pro	Leu	Ala	Arg	Ala	Ser	Ile	Lys	Ser	Ala	Lys	
				440					445					450		
GTA	GAC	GGG	GTC	TCT	TAT	TTC	CGG	CAC	AAG	GAA	AGG	CTT	CTG	CGC	ATC	1566
Val	Asp	Gly	Val	Ser	Tyr	Phe	Arg	His	Lys	Glu	Arg	Leu	Leu	Arg	Ile	
			455					460					465			
TCC	ATT	CGC	CAC	ATG	GTT	AAA	TCC	CAG	GTG	TTT	TAC	TGG	ATT	GTG	CTG	1614
Ser	Ile	Arg	His	Met	Val	Lys	Ser	Gln	Val	Phe	Tyr	Trp	Ile	Val	Leu	
		470					475					480				
AGC	CTT	GTG	GCA	CTC	AAC	ACT	GCC	TGT	GTG	GCC	ATT	GTC	CAT	CAC	AAC	1662
Ser	Leu	Val	Ala	Leu	Asn	Thr	Ala	Cys	Val	Ala	Ile	Val	His	His	Asn	
	485					490					495					

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CAG Gln 500	CCC Pro	CAG Gln	TGG Trp	CTC Leu	ACC Thr 505	CAC His	CTC Leu	CTC Leu	TAC Tyr	TAT Tyr 510	GCA Ala	GAA Glu	TTT Phe	CTG Leu	TTT Phe 515	1710
CTG Leu	GGA Gly	CTC Leu	TTC Phe	CTC Leu 520	TTG Leu	GAG Glu	ATG Met	TCC Ser	CTG Leu 525	AAG Lys	ATG Met	TAT Tyr	GGC Gly	ATG Met 530	GGG Gly	1758
CCT Pro	CGC Arg	CTT Leu	TAT Tyr 535	TTT Phe	CAC His	TCT Ser	TCA Ser	TTC Phe 540	AAC Asn	TGC Cys	TTT Phe	GAT Asp	TTT Phe 545	GGG Gly	GTC Val	1806
ACA Thr	GTG Val	GGC Gly 550	AGT Ser	ATC Ile	TTT Phe	GAA Glu	GTG Val 555	GTC Val	TGG Trp	GCA Ala	ATC Ile	TTC Phe 560	AGA Arg	CCT Pro	GGT Gly	1854
ACG Thr	TCT Ser 565	TTT Phe	GGA Gly	ATC Ile	AGT Ser	GTC Val 570	TTG Leu	CGA Arg	GCC Ala	CTC Leu	CGG Arg 575	CTT Leu	CTA Leu	AGA Arg	ATA Ile	1902
TTT Phe 580	AAA Lys	ATA Ile	ACC Thr	AAG Lys	TAT Tyr 585	TGG Trp	GCT Ala	TCC Ser	CTA Leu	CGG Arg 590	AAT Asn	TTG Leu	GTG Val	GTC Val	TCC Ser 595	1950
TTG Leu	ATG Met	AGC Ser	TCA Ser	ATG Met 600	AAG Lys	TCT Ser	ATC Ile	ATC Ile	AGT Ser 605	TTG Leu	CTT Leu	TTC Phe	CTC Leu 610	CTC Leu	TTC Phe	1998
CTC Leu	TTC Phe	ATC Ile	GTT Val 615	GTC Val	TTT Phe	GCT Ala	CTC Leu 620	CTA Leu	GGA Gly	ATG Met	CAG Gln	TTA Leu	TTT Phe 625	GGA Gly	GGC Gly	2046
AGG Arg	TTT Phe 630	AAC Asn	TTT Phe	AAT Asn	GAT Asp	GGG Gly	ACT Thr 635	CCT Pro	TCG Ser	GCA Ala	AAT Asn 640	TTT Phe	GAT Asp	ACC Thr	TTC Phe	2094
CCT Pro	GCA Ala 645	GCC Ala	ATC Ile	ATG Met	ACT Thr	GTG Val 650	TTC Phe	CAG Gln	ATC Ile	CTG Leu	ACG Thr 655	GGT Gly	GAG Glu	GAC Asp	TGG Trp	2142
AAT Asn 660	GAG Glu	GTG Val	ATG Met	TAC Tyr	AAT Asn 665	GGG Gly	ATC Ile	CGC Arg	TCC Ser	CAG Gln 670	GGT Gly	GGG Gly	GTC Val	AGC Ser	TCA Ser 675	2190
GGC Gly	ATG Met	TGG Trp	TCT Ser	GCC Ala 680	ATC Ile	TAC Tyr	TTC Phe	ATT Ile	GTG Val 685	CTC Leu	ACC Thr	TTG Leu	TTT Phe 690	GGC Gly	AAC Asn	2238
TAC Tyr	ACG Thr	CTA Leu	CTG Leu	AAT Asn 695	GTG Val	TTC Phe	TTG Leu	GCT Ala 700	ATC Ile	GCT Ala	GTG Val	GAT Asp	AAT Asn 705	CTC Leu	GCC Ala	2286
AAC Asn	GCC Ala	CAG Gln 710	GAA Glu	CTG Leu	ACC Thr	AAG Lys	GAT Asp 715	GAA Glu	CAG Gln	GAG Glu	GAA Glu	GAA Glu 720	GAG Glu	GCC Ala	TTC Phe	2334

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AAC Asn	CAG Gln	AAA Lys	CAT His	GCA Ala	CTG Leu	CAG Gln	AAG Lys	GCC Ala	AAG Lys	GAG Glu	GTC Val	AGC Ser	CCG Pro	ATG Met	TCT Ser	2382
725						730					735					
GCA Ala	CCC Pro	AAC Asn	ATG Met	CCT Pro	TCG Ser	ATC Ile	GAG Glu	AGG Arg	GAG Glu	CGG Arg	AGG Arg	CGC Arg	CGG Arg	CAC His	CAC His	2430
740					745					750					755	
ATG Met	TCC Ser	GTG Val	TGG Trp	GAG Glu	CAG Gln	CGT Arg	ACC Thr	AGC Ser	CAG Gln	CTG Leu	AGG Arg	AAG Lys	CAC His	ATG Met	CAG Gln	2478
				760					765					770		
ATG Met	TCC Ser	AGC Ser	CAG Gln	GAG Glu	GCC Ala	CTC Leu	AAC Asn	AGA Arg	GAG Glu	GAG Glu	GCG Ala	CCG Pro	ACC Thr	ATG Met	AAC Asn	2526
			775					780					785			
CCG Pro	CTC Leu	AAC Asn	CCC Pro	CTC Leu	AAC Asn	CCG Pro	CTC Leu	AGC Ser	TCC Ser	CTC Leu	AAC Asn	CCG Pro	CTC Leu	AAT Asn	GCC Ala	2574
		790					795					800				
CAC His	CCC Pro	AGC Ser	CTT Leu	TAT Tyr	CGG Arg	CGA Arg	CCC Pro	AGG Arg	GCC Ala	ATT Ile	GAG Glu	GGC Gly	CTG Leu	GCC Ala	CTG Leu	2622
	805					810					815					
GGC Gly	CTG Leu	GCC Ala	CTG Leu	GAG Glu	AAG Lys	TTC Phe	GAG Glu	GAG Glu	GAG Glu	CGC Arg	ATC Ile	AGC Ser	CGT Arg	GGG Gly	GGG Gly	2670
820					825					830					835	
TCC Ser	CTC Leu	AAG Lys	GGG Gly	GAT Asp	GGA Gly	GGG Gly	GAC Asp	CGA Arg	TCC Ser	AGT Ser	GCC Ala	CTG Leu	GAC Asp	AAC Asn	CAG Gln	2718
				840					845					850		
AGG Arg	ACC Thr	CCT Pro	TTG Leu	TCC Ser	CTG Leu	GGC Gly	CAG Gln	CGG Arg	GAG Glu	CCA Pro	CCA Pro	TGG Trp	CTG Leu	GCC Ala	AGG Arg	2766
			855					860					865			
CCC Pro	TGT Cys	CAT His	GGA Gly	AAC Asn	TGT Cys	GAC Asp	CCG Pro	ACT Thr	CAG Gln	CAG Gln	GAG Glu	GCA Ala	GGG Gly	GGA Gly	GGA Gly	2814
		870					875					880				
GAG Glu	GCT Ala	GTG Val	GTG Val	ACC Thr	TTT Phe	GAG Glu	GAC Asp	CGG Arg	GCC Ala	AGG Arg	CAC His	AGG Arg	CAG Gln	AGC Ser	CAA Gln	2862
	885					890					895					
CGG Arg	CGC Arg	AGC Ser	CGG Arg	CAT His	CGC Arg	CGC Arg	GTC Val	AGG Arg	ACA Thr	GAA Glu	GGC Gly	AAG Lys	GAG Glu	TCC Ser	TCT Ser	2910
900					905					910					915	
TCA Ser	GCC Ala	TCC Ser	CGG Arg	AGC Ser	AGG Arg	TCT Ser	GCC Ala	AGC Ser	CAG Gln	GAA Glu	CGC Arg	AGT Ser	CTG Leu	GAT Asp	GAA Glu	2958
				920					925					930		
GCC Ala	ATG Met	CCC Pro	ACT Thr	GAA Glu	GGG Gly	GAG Glu	AAG Lys	GAC Asp	CAT His	GAG Glu	CTC Leu	AGG Arg	GGC Gly	AAC Asn	CAT His	3006
			935					940					945			

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GGT	GCC	AAG	GAG	CCA	ACG	ATC	CAA	GAA	GAG	AGA	GCC	CAG	GAT	TTA	AGG	3054
Gly	Ala	Lys	Glu	Pro	Thr	Ile	Gln	Glu	Glu	Arg	Ala	Gln	Asp	Leu	Arg	
		950					955					960				
AGG	ACC	AAC	AGT	CTG	ATG	GTG	TCC	AGA	GGC	TCC	GGG	CTG	GCA	GGA	GGC	3102
Arg	Thr	Asn	Ser	Leu	Met	Val	Ser	Arg	Gly	Ser	Gly	Leu	Ala	Gly	Gly	
	965					970					975					
CTT	GAT	GAG	GCT	GAC	ACC	CCC	CTA	GTC	CTG	CCC	CAT	CCT	GAG	CTG	GAA	3150
Leu	Asp	Glu	Ala	Asp	Thr	Pro	Leu	Val	Leu	Pro	His	Pro	Glu	Leu	Glu	
980					985					990					995	
GTG	GGG	AAG	CAC	GTG	GTG	CTG	ACG	GAG	CAG	GAG	CCA	GAA	GGC	AGC	AGT	3198
Val	Gly	Lys	His	Val	Val	Leu	Thr	Glu	Gln	Glu	Pro	Glu	Gly	Ser	Ser	
				1000					1005					1010		
GAG	CAG	GCC	CTG	CTG	GGG	AAT	GTG	CAG	CTA	GAC	ATG	GGC	CGG	GTC	ATC	3246
Glu	Gln	Ala	Leu	Leu	Gly	Asn	Val	Gln	Leu	Asp	Met	Gly	Arg	Val	Ile	
			1015					1020					1025			
AGC	CAG	AGC	GAG	CCT	GAC	CTC	TCC	TGC	ATC	ACG	GCC	AAC	ACG	GAC	AAG	3294
Ser	Gln	Ser	Glu	Pro	Asp	Leu	Ser	Cys	Ile	Thr	Ala	Asn	Thr	Asp	Lys	
		1030					1035					1040				
GCC	ACC	ACC	GAG	AGC	ACC	AGC	GTC	ACC	GTC	GCC	ATC	CCC	GAC	GTG	GAC	3342
Ala	Thr	Thr	Glu	Ser	Thr	Ser	Val	Thr	Val	Ala	Ile	Pro	Asp	Val	Asp	
	1045					1050					1055					
CCC	TTG	GTG	GAC	TCA	ACC	GTG	GTG	CAC	ATT	AGC	AAC	AAG	ACG	GAT	GGG	3390
Pro	Leu	Val	Asp	Ser	Thr	Val	Val	His	Ile	Ser	Asn	Lys	Thr	Asp	Gly	
1060					1065					1070					1075	
GAA	GCC	AGT	CCC	TTG	AAG	GAG	GCA	GAG	ATC	AGA	GAG	GAT	GAG	GAG	GAG	3438
Glu	Ala	Ser	Pro	Leu	Lys	Glu	Ala	Glu	Ile	Arg	Glu	Asp	Glu	Glu	Glu	
				1080					1085					1090		
GTG	GAG	AAG	AAG	AAG	CAG	AAG	AAG	GAG	AAG	CGT	GAG	ACA	GGC	AAA	GCC	3486
Val	Glu	Lys	Lys	Lys	Gln	Lys	Lys	Glu	Lys	Arg	Glu	Thr	Gly	Lys	Ala	
			1095					1100					1105			
ATG	GTG	CCC	CAC	AGC	TCA	ATG	TTC	ATC	TTC	AGC	ACC	ACC	AAC	CCG	ATC	3534
Met	Val	Pro	His	Ser	Ser	Met	Phe	Ile	Phe	Ser	Thr	Thr	Asn	Pro	Ile	
		1110					1115					1120				
CGG	AGG	GCC	TGC	CAC	TAC	ATC	GTG	AAC	CTG	CGC	TAC	TTT	GAG	ATG	TGC	3582
Arg	Arg	Ala	Cys	His	Tyr	Ile	Val	Asn	Leu	Arg	Tyr	Phe	Glu	Met	Cys	
	1125					1130					1135					
ATC	CTC	CTG	GTG	ATT	GCA	GCC	AGC	AGC	ATC	GCC	CTG	GCG	GCA	GAG	GAC	3630
Ile	Leu	Leu	Val	Ile	Ala	Ala	Ser	Ser	Ile	Ala	Leu	Ala	Ala	Glu	Asp	
1140					1145					1150				1155		
CCC	GTC	CTG	ACC	AAC	TCG	GAG	CGC	AAC	AAA	GTC	CTG	AGG	TAT	TTT	GAC	3678
Pro	Val	Leu	Thr	Asn	Ser	Glu	Arg	Asn	Lys	Val	Leu	Arg	Tyr	Phe	Asp	
				1160					1165					1170		

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TAT	GTG	TTC	ACG	GGC	GTG	TTC	ACC	TTT	GAG	ATG	GTT	ATA	AAG	ATG	ATA	3726
Tyr	Val	Phe	Thr	Gly	Val	Phe	Thr	Phe	Glu	Met	Val	Ile	Lys	Met	Ile	
			1175					1180					1185			
GAC	CAA	GGC	TTG	ATC	CTG	CAG	GAT	GGG	TCC	TAC	TTC	CGA	GAC	TTG	TGG	3774
Asp	Gln	Gly	Leu	Ile	Leu	Gln	Asp	Gly	Ser	Tyr	Phe	Arg	Asp	Leu	Trp	
		1190					1195					1200				
AAC	ATC	CTG	GAC	TTT	GTG	GTG	GTC	GTT	GGC	GCA	TTG	GTG	GCC	TTT	GCT	3822
Asn	Ile	Leu	Asp	Phe	Val	Val	Val	Val	Gly	Ala	Leu	Val	Ala	Phe	Ala	
	1205					1210					1215					
CTG	GCG	AAC	GCT	TTG	GGA	ACC	AAC	AAA	GGA	CGG	GAC	ATC	AAG	ACC	ATC	3870
Leu	Ala	Asn	Ala	Leu	Gly	Thr	Asn	Lys	Gly	Arg	Asp	Ile	Lys	Thr	Ile	
1220					1225				1230						1235	
AAG	TCT	CTG	CGG	GTG	CTC	CGA	GTT	CTA	AGG	CCA	CTG	AAA	ACC	ATC	AAG	3918
Lys	Ser	Leu	Arg	Val	Leu	Arg	Val	Leu	Arg	Pro	Leu	Lys	Thr	Ile	Lys	
			1240						1245					1250		
CGC	TTG	CCC	AAG	CTC	AAG	GCC	GTC	TTC	GAC	TGC	GTA	GTG	ACC	TCC	TTG	3966
Arg	Leu	Pro	Lys	Leu	Lys	Ala	Val	Phe	Asp	Cys	Val	Val	Thr	Ser	Leu	
			1255					1260					1265			
AAG	AAT	GTC	TTC	AAC	ATA	CTC	ATT	GTG	TAC	AAG	CTC	TTC	ATG	TTC	ATC	4014
Lys	Asn	Val	Phe	Asn	Ile	Leu	Ile	Val	Tyr	Lys	Leu	Phe	Met	Phe	Ile	
		1270					1275					1280				
TTT	GCT	GTC	ATC	GCA	GTT	CAG	CTC	TTC	AAG	GGA	AAG	TTC	TTT	TAT	TGC	4062
Phe	Ala	Val	Ile	Ala	Val	Gln	Leu	Phe	Lys	Gly	Lys	Phe	Phe	Tyr	Cys	
	1285					1290					1295					
ACG	GAC	AGT	TCC	AAG	GAC	ACA	GAG	AAG	GAG	TGC	ATA	GGC	AAC	TAT	GTA	4110
Thr	Asp	Ser	Ser	Lys	Asp	Thr	Glu	Lys	Glu	Cys	Ile	Gly	Asn	Tyr	Val	
1300					1305					1310					1315	
GAT	CAC	GAG	AAA	AAC	AAG	ATG	GAG	GTG	AAG	GGC	CGG	GAA	TGG	AAG	CGC	4158
Asp	His	Glu	Lys	Asn	Lys	Met	Glu	Val	Lys	Gly	Arg	Glu	Trp	Lys	Arg	
				1320					1325					1330		
CAT	GAA	TTC	CAC	TAC	GAC	AAC	ATT	ATC	TGG	GCC	CTG	CTG	ACC	CTC	TTC	4206
His	Glu	Phe	His	Tyr	Asp	Asn	Ile	Ile	Trp	Ala	Leu	Leu	Thr	Leu	Phe	
			1335					1340					1345			
ACC	GTC	TCC	ACA	GGG	GAA	GGA	TGG	CCT	CAA	GTT	CTG	CAG	CAC	TCT	GTA	4254
Thr	Val	Ser	Thr	Gly	Glu	Gly	Trp	Pro	Gln	Val	Leu	Gln	His	Ser	Val	
		1350					1355					1360				
GAT	GTG	ACA	GAG	GAA	GAC	CGA	GGC	CCA	AGC	CGC	AGC	AAC	CGC	ATG	GAG	4302
Asp	Val	Thr	Glu	Glu	Asp	Arg	Gly	Pro	Ser	Arg	Ser	Asn	Arg	Met	Glu	
		1365				1370					1375					
ATG	TCT	ATC	TTT	TAT	GTA	GTC	TAC	TTT	GTG	GTC	TTC	CCC	TTC	TTC	TTT	4350
Met	Ser	Ile	Phe	Tyr	Val	Val	Tyr	Phe	Val	Val	Phe	Pro	Phe	Phe	Phe	
1380					1385				1390						1395	

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GTC	AAT	ATC	TTT	GTG	GCT	CTC	ATC	ATC	ATC	ACC	TTC	CAG	GAG	CAA	GGG	4398
Val	Asn	Ile	Phe	Val	Ala	Leu	Ile	Ile	Ile	Thr	Phe	Gln	Glu	Gln	Gly	
				1400						1405					1410	
GAT	AAG	ATG	ATG	GAG	GAG	TGC	AGC	CTG	GAG	AAG	AAT	GAG	AGG	GCG	TGC	4446
Asp	Lys	Met	Met	Glu	Glu	Cys	Ser	Leu	Glu	Lys	Asn	Glu	Arg	Ala	Cys	
			1415					1420						1425		
ATC	GAC	TTC	GCC	ATC	AGC	GCC	AAA	CCT	CTC	ACC	CGC	TAC	ATG	CCG	CAG	4494
Ile	Asp	Phe	Ala	Ile	Ser	Ala	Lys	Pro	Leu	Thr	Arg	Tyr	Met	Pro	Gln	
		1430					1435						1440			
AAC	AGA	CAC	ACC	TTC	CAG	TAC	CGC	GTG	TGG	CAC	TTT	GTG	GTG	TCT	CCG	4542
Asn	Arg	His	Thr	Phe	Gln	Tyr	Arg	Val	Trp	His	Phe	Val	Val	Ser	Pro	
	1445					1450					1455					
TCC	TTT	GAG	TAC	ACC	ATT	ATG	GCC	ATG	ATC	GCC	TTG	AAT	ACT	GTT	GTG	4590
Ser	Phe	Glu	Tyr	Thr	Ile	Met	Ala	Met	Ile	Ala	Leu	Asn	Thr	Val	Val	
1460					1465					1470					1475	
CTG	ATG	ATG	AAG	TAT	TAT	TCT	GCT	CCC	TGT	ACC	TAT	GAG	CTG	GCC	CTG	4638
Leu	Met	Met	Lys	Tyr	Tyr	Ser	Ala	Pro	Cys	Thr	Tyr	Glu	Leu	Ala	Leu	
			1480						1485					1490		
AAG	TAC	CTG	AAT	ATC	GCC	TTC	ACC	ATG	GTG	TTT	TCC	CTG	GAA	TGT	GTC	4686
Lys	Tyr	Leu	Asn	Ile	Ala	Phe	Thr	Met	Val	Phe	Ser	Leu	Glu	Cys	Val	
			1495					1500					1505			
CTG	AAG	GTC	ATC	GCT	TTT	GGC	TTT	TTG	AAC	TAT	TTC	CGA	GAC	ACC	TGG	4734
Leu	Lys	Val	Ile	Ala	Phe	Gly	Phe	Leu	Asn	Tyr	Phe	Arg	Asp	Thr	Trp	
		1510				1515						1520				
AAT	ATC	TTT	GAC	TTC	ATC	ACC	GTG	ATT	GGC	AGT	ATC	ACA	GAA	ATT	ATC	4782
Asn	Ile	Phe	Asp	Phe	Ile	Thr	Val	Ile	Gly	Ser	Ile	Thr	Glu	Ile	Ile	
	1525					1530					1535					
CTG	ACA	GAC	AGC	AAG	CTG	GTG	AAC	ACC	AGT	GGC	TTC	AAT	ATG	AGC	TTT	4830
Leu	Thr	Asp	Ser	Lys	Leu	Val	Asn	Thr	Ser	Gly	Phe	Asn	Met	Ser	Phe	
1540					1545					1550					1555	
CTG	AAG	CTC	TTC	CGA	GCT	GCC	CGC	CTC	ATA	AAG	CTC	CTG	CGT	CAG	GGC	4878
Leu	Lys	Leu	Phe	Arg	Ala	Ala	Arg	Leu	Ile	Lys	Leu	Leu	Arg	Gln	Gly	
			1560					1565						1570		
TAT	ACC	ATA	CGC	ATT	TTG	CTG	TGG	ACC	TTT	GTG	CAG	TCC	TTT	AAG	GCC	4926
Tyr	Thr	Ile	Arg	Ile	Leu	Leu	Trp	Thr	Phe	Val	Gln	Ser	Phe	Lys	Ala	
			1575				1580						1585			
CTC	CCT	TAT	GTC	TGC	CTT	TTA	ATT	GCC	ATG	CTT	TTC	TTC	ATT	TAT	GCC	4974
Leu	Pro	Tyr	Val	Cys	Leu	Leu	Ile	Ala	Met	Leu	Phe	Phe	Ile	Tyr	Ala	
		1590				1595						1600				
ATC	ATT	GGG	ATG	CAG	GTA	TTT	GGA	AAC	ATA	AAA	TTA	GAC	GAG	GAG	AGT	5022
Ile	Ile	Gly	Met	Gln	Val	Phe	Gly	Asn	Ile	Lys	Leu	Asp	Glu	Glu	Ser	
	1605					1610					1615					

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CAC	ATC	AAC	CGG	CAC	AAC	AAC	TTC	CGG	AGT	TTC	TTT	GGG	TCC	CTA	ATG	5070
His	Ile	Asn	Arg	His	Asn	Asn	Phe	Arg	Ser	Phe	Phe	Gly	Ser	Leu	Met	
1620					1625					1630					1635	
CTA	CTC	TTC	AGG	AGT	GCC	ACA	GGT	GAG	GCC	TGG	CAG	GAG	ATT	ATG	CTG	5118
Leu	Leu	Phe	Arg	Ser	Ala	Thr	Gly	Glu	Ala	Trp	Gln	Glu	Ile	Met	Leu	
				1640					1645					1650		
TCA	TGC	CTT	GGG	GAG	AAG	GGC	TGT	GAG	CCT	GAC	ACC	ACC	GCA	CCA	TCA	5166
Ser	Cys	Leu	Gly	Glu	Lys	Gly	Cys	Glu	Pro	Asp	Thr	Thr	Ala	Pro	Ser	
			1655					1660					1665			
GGG	CAG	AAC	GAG	AAT	GAA	CGC	TGC	GGC	ACC	GAT	CTG	GCC	TAC	GTG	TAC	5214
Gly	Gln	Asn	Glu	Asn	Glu	Arg	Cys	Gly	Thr	Asp	Leu	Ala	Tyr	Val	Tyr	
		1670					1675					1680				
TTT	GTC	TCC	TTC	ATC	TTC	TTC	TGC	TCC	TTC	TTG	ATG	CTC	AAC	CTG	TTT	5262
Phe	Val	Ser	Phe	Ile	Phe	Phe	Cys	Ser	Phe	Leu	Met	Leu	Asn	Leu	Phe	
	1685					1690					1695					
GTG	GCC	GTC	ATC	ATG	GAC	AAC	TTT	GAG	TAC	CTG	ACT	CGG	GAC	TCC	TCC	5310
Val	Ala	Val	Ile	Met	Asp	Asn	Phe	Glu	Tyr	Leu	Thr	Arg	Asp	Ser	Ser	
1700					1705					1710					1715	
ATC	CTG	GGG	CCT	CAC	CAC	TTG	GAC	GAG	TTT	GTC	CGC	GTC	TGG	GCA	GAA	5358
Ile	Leu	Gly	Pro	His	His	Leu	Asp	Glu	Phe	Val	Arg	Val	Trp	Ala	Glu	
				1720					1725					1730		
TAT	GAC	CGA	GCA	GCA	TGT	GGC	CGC	ATC	CAT	TAC	ACT	GAG	ATG	TAT	GAA	5406
Tyr	Asp	Arg	Ala	Ala	Cys	Gly	Arg	Ile	His	Tyr	Thr	Glu	Met	Tyr	Glu	
			1735					1740					1745			
ATG	CTG	ACT	CTC	ATG	TCA	CCT	CCG	CTA	GGC	CTC	GGC	AAG	AGA	TGT	CCC	5454
Met	Leu	Thr	Leu	Met	Ser	Pro	Pro	Leu	Gly	Leu	Gly	Lys	Arg	Cys	Pro	
		1750				1755						1760				
TCC	AAA	GTG	GCA	TAT	AAG	AGG	TTG	GTC	CTG	ATG	AAC	ATG	CCA	GTA	GCT	5502
Ser	Lys	Val	Ala	Tyr	Lys	Arg	Leu	Val	Leu	Met	Asn	Met	Pro	Val	Ala	
	1765					1770					1775					
GAG	GAC	ATG	ACG	GTC	CAC	TTC	ACC	TCC	ACA	CTT	ATG	GCT	CTG	ATC	CGG	5550
Glu	Asp	Met	Thr	Val	His	Phe	Thr	Ser	Thr	Leu	Met	Ala	Leu	Ile	Arg	
1780					1785					1790				1795		
ACA	GCT	CTG	GAC	ATT	AAA	ATT	GCC	AAA	GGT	GGT	GCA	GAC	AGG	CAG	CAG	5598
Thr	Ala	Leu	Asp	Ile	Lys	Ile	Ala	Lys	Gly	Gly	Ala	Asp	Arg	Gln	Gln	
				1800					1805					1810		
CTA	GAC	TCA	GAG	CTA	CAA	AAG	GAG	ACC	CTA	GCC	ATC	TGG	CCT	CAC	CTA	5646
Leu	Asp	Ser	Glu	Leu	Gln	Lys	Glu	Thr	Leu	Ala	Ile	Trp	Pro	His	Leu	
			1815					1820					1825			
TCC	CAG	AAG	ATG	CTG	GAT	CTG	CTT	GTG	CCC	ATG	CCC	AAA	GCC	TCT	GAC	5694
Ser	Gln	Lys	Met	Leu	Asp	Leu	Leu	Val	Pro	Met	Pro	Lys	Ala	Ser	Asp	
		1830					1835					1840				

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CTG	ACT	GTG	GGC	AAA	ATC	TAT	GCA	GCA	ATG	ATG	ATC	ATG	GAC	TAC	TAT	5742
Leu	Thr	Val	Gly	Lys	Ile	Tyr	Ala	Ala	Met	Met	Ile	Met	Asp	Tyr	Tyr	
1845						1850					1855					
AAG	CAG	AGT	AAG	GTG	AAG	AAG	CAG	AGG	CAG	CAG	CTG	GAG	GAA	CAG	AAA	5790
Lys	Gln	Ser	Lys	Val	Lys	Lys	Gln	Arg	Gln	Gln	Leu	Glu	Glu	Gln	Lys	
1860					1865				1870						1875	
AAT	GCC	CCC	ATG	TTC	CAG	CGC	ATG	GAG	CCT	TCA	TCT	CTG	CCT	CAG	GAG	5838
Asn	Ala	Pro	Met	Phe	Gln	Arg	Met	Glu	Pro	Ser	Ser	Leu	Pro	Gln	Glu	
				1880					1885					1890		
ATC	ATT	GCT	AAT	GCC	AAA	GCC	CTG	CCT	TAC	CTC	CAG	CAG	GAC	CCC	GTT	5886
Ile	Ile	Ala	Asn	Ala	Lys	Ala	Leu	Pro	Tyr	Leu	Gln	Gln	Asp	Pro	Val	
			1895					1900					1905			
TCA	GGC	CTG	AGT	GGC	CGG	AGT	GGA	TAC	CCT	TCG	ATG	AGT	CCA	CTC	TCT	5934
Ser	Gly	Leu	Ser	Gly	Arg	Ser	Gly	Tyr	Pro	Ser	Met	Ser	Pro	Leu	Ser	
	1910						1915					1920				
CCC	CAG	GAT	ATA	TTC	CAG	TTG	GCT	TGT	ATG	GAC	CCC	GCC	GAT	GAC	GGA	5982
Pro	Gln	Asp	Ile	Phe	Gln	Leu	Ala	Cys	Met	Asp	Pro	Ala	Asp	Asp	Gly	
1925						1930					1935					
CAG	TTC	CAA	GAA	CGG	CAG	TCT	CTG	GTG	GTG	ACA	GAC	CCT	AGC	TCC	ATG	6030
Gln	Phe	Gln	Glu	Arg	Gln	Ser	Leu	Val	Val	Thr	Asp	Pro	Ser	Ser	Met	
1940					1945					1950					1955	
AGA	CGT	TCA	TTT	TCC	ACT	ATT	CGG	GAT	AAG	CGT	TCA	AAT	TCC	TCG	TGG	6078
Arg	Arg	Ser	Phe	Ser	Thr	Ile	Arg	Asp	Lys	Arg	Ser	Asn	Ser	Ser	Trp	
				1960					1965					1970		
TTG	GAG	GAA	TTC	TCC	ATG	GAG	CGA	AGC	AGT	GAA	AAT	ACC	TAC	AAG	TCC	6126
Leu	Glu	Glu	Phe	Ser	Met	Glu	Arg	Ser	Ser	Glu	Asn	Thr	Tyr	Lys	Ser	
			1975					1980					1985			
CGT	CGC	CGG	AGT	TAC	CAC	TCC	TCC	TTG	CGG	CTG	TCA	GCC	CAC	CGC	CTG	6174
Arg	Arg	Arg	Ser	Tyr	His	Ser	Ser	Leu	Arg	Leu	Ser	Ala	His	Arg	Leu	
			1990				1995					2000				
AAC	TCT	GAT	TCA	GGC	CAC	AAG	TCT	GAC	ACT	CAC	CCC	TCA	GGG	GGC	AGG	6222
Asn	Ser	Asp	Ser	Gly	His	Lys	Ser	Asp	Thr	His	Pro	Ser	Gly	Gly	Arg	
2005						2010					2015					
GAG	CGG	CGA	CGA	TCA	AAA	GAG	CGA	AAG	CAT	CTT	CTC	TCT	CCT	GAT	GTC	6270
Glu	Arg	Arg	Arg	Ser	Lys	Glu	Arg	Lys	His	Leu	Leu	Ser	Pro	Asp	Val	
2020					2025				2030						2035	
TCC	CGC	TGC	AAT	TCA	GAA	GAG	CGA	GGG	ACC	CAG	GCT	GAC	TGG	GAG	TCC	6318
Ser	Arg	Cys	Asn	Ser	Glu	Glu	Arg	Gly	Thr	Gln	Ala	Asp	Trp	Glu	Ser	
				2040				2045						2050		
CCA	GAG	CGC	CGT	CAA	TCC	AGG	TCA	CCC	AGT	GAG	GGC	AGG	TCA	CAG	ACG	6366
Pro	Glu	Arg	Arg	Gln	Ser	Arg	Ser	Pro	Ser	Glu	Gly	Arg	Ser	Gln	Thr	
			2055					2060					2065			

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CCC AAC AGA CAG GGC ACA GGT TCC CTA AGT GAG AGC TCC ATC CCC TCT Pro Asn Arg Gln Gly Thr Gly Ser Leu Ser Glu Ser Ser Ile Pro Ser 2070 2075 2080	6414
GTC TCT GAC ACC AGC ACC CCA AGA AGA AGT CGT CGG CAG CTC CCA CCC Val Ser Asp Thr Ser Thr Pro Arg Arg Ser Arg Arg Gln Leu Pro Pro 2085 2090 2095	6462
GTC CCG CCA AAG CCC CGG CCC CTC CTT TCC TAC AGC TCC CTG ATT CGA Val Pro Pro Lys Pro Arg Pro Leu Leu Ser Tyr Ser Ser Leu Ile Arg 2100 2105 2110 2115	6510
CAC GCG GGC AGC ATC TCT CCA CCT GCT GAT GGA AGC GAG GAG GGC TCC His Ala Gly Ser Ile Ser Pro Pro Ala Asp Gly Ser Glu Glu Gly Ser 2120 2125 2130	6558
CCG CTG ACC TCC CAA GCT CTG GAG AGC AAC AAT GCT TGG CTG ACC GAG Pro Leu Thr Ser Gln Ala Leu Glu Ser Asn Asn Ala Trp Leu Thr Glu 2135 2140 2145	6606
TCT TCC AAC TCT CCG CAC CCC CAG CAG AGG CAA CAT GCC TCC CCA CAG Ser Ser Asn Ser Pro His Pro Gln Gln Arg Gln His Ala Ser Pro Gln 2150 2155 2160	6654
CGC TAC ATC TCC GAG CCC TAC TTG GCC CTG CAC GAA GAC TCC CAC GCC Arg Tyr Ile Ser Glu Pro Tyr Leu Ala Leu His Glu Asp Ser His Ala 2165 2170 2175	6702
TCA GAC TGT GTT GAG GAG GAG ACG CTC ACT TTC GAA GCA GCC GTG GCT Ser Asp Cys Val Glu Glu Glu Thr Leu Thr Phe Glu Ala Ala Val Ala 2180 2185 2190 2195	6750
ACT AGC CTG GGC CGT TCC AAC ACC ATC GGC TCA GCC CCA CCC CTG CGG Thr Ser Leu Gly Arg Ser Asn Thr Ile Gly Ser Ala Pro Pro Leu Arg 2200 2205 2210	6798
CAT AGC TGG CAG ATG CCC AAC GGG CAC TAT CGG CGG CGG AGG CGC GGG His Ser Trp Gln Met Pro Asn Gly His Tyr Arg Arg Arg Arg Arg Gly 2215 2220 2225	6846
GGG CCT GGG CCA GGC ATG ATG TGT GGG GCT GTC AAC AAC CTG CTA AGT Gly Pro Gly Pro Gly Met Met Cys Gly Ala Val Asn Asn Leu Leu Ser 2230 2235 2240	6894
GAC ACG GAA GAA GAT GAC AAA TGC TAGAGGCTGC TCCCCCTCC GATGCATGCT Asp Thr Glu Glu Asp Asp Lys Cys 2245 2250	6948
CTTCTCTCAC ATGGAGAAAA CCAAGACAGA ATTGGGAAGC CAGTGCGGCC CCGCGGGGAG	7008
GAAGAGGGAA AAGGAAGATG GAAG	7032

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7089 base pairs

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(B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: CDS
 (B) LOCATION: 166..6978
 (D) OTHER INFORMATION: /standard_name= "Alpha-1E-3"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GCTGCTGCTG CCTCTCCGAA GAGCTCGCGG AGCTCCCCAG AGGCGGTGGT CCCCGTGCTT	60
GTCTGGATGC GGCTCTGAGT CTCCGTGTGT CTTTCTGCTT GTTGCTGTGT GCGGGTGTTT	120
GGCCGCGATC ACCTTTGTGT GTCTTCTGTC TGTTTAAACC TCAGG ATG GCT CGC	174
Met Ala Arg	
1	
TTC GGG GAG GCG GTG GTC GCC AGG CCA GGG TCC GGC GAT GGA GAC TCG	222
Phe Gly Glu Ala Val Val Ala Arg Pro Gly Ser Gly Asp Gly Asp Ser	
5 10 15	
GAC CAG AGC AGG AAC CGG CAA GGA ACC CCC GTG CCG GCC TCG GGG CAG	270
Asp Gln Ser Arg Asn Arg Gln Gly Thr Pro Val Pro Ala Ser Gly Gln	
20 25 30 35	
GCG GCC GCC TAC AAG CAG ACG AAA GCA CAG AGG GCG CGG ACT ATG GCT	318
Ala Ala Ala Tyr Lys Gln Thr Lys Ala Gln Arg Ala Arg Thr Met Ala	
40 45 50	
TTG TAC AAC CCC ATT CCC GTC CGG CAG AAC TGT TTC ACC GTC AAC AGA	366
Leu Tyr Asn Pro Ile Pro Val Arg Gln Asn Cys Phe Thr Val Asn Arg	
55 60 65	
TCC CTG TTC ATC TTC GGA GAA GAT AAC ATT GTC AGG AAA TAT GCC AAG	414
Ser Leu Phe Ile Phe Gly Glu Asp Asn Ile Val Arg Lys Tyr Ala Lys	
70 75 80	
AAG CTC ATC GAT TGG CCG CCA TTT GAG TAC ATG ATC CTG GCC ACC ATC	462
Lys Leu Ile Asp Trp Pro Pro Phe Glu Tyr Met Ile Leu Ala Thr Ile	
85 90 95	
ATT GCC AAC TGC ATC GTC CTG GCC CTG GAG CAG CAT CTT CCT GAG GAT	510
Ile Ala Asn Cys Ile Val Leu Ala Leu Glu Gln His Leu Pro Glu Asp	
100 105 110 115	
GAC AAG ACC CCC ATG TCC CGA AGA CTG GAG AAG ACA GAA CCT TAT TTC	558
Asp Lys Thr Pro Met Ser Arg Arg Leu Glu Lys Thr Glu Pro Tyr Phe	
120 125 130	
ATT GGG ATC TTT TGC TTT GAA GCT GGG ATC AAA ATT GTG GCC CTG GGG	606

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Ile	Gly	Ile	Phe 135	Cys	Phe	Glu	Ala	Gly 140	Ile	Lys	Ile	Val	Ala 145	Leu	Gly		
TTC	ATC	TTC	CAT	AAG	GGC	TCT	TAC	CTC	CGC	AAT	GGC	TGG	AAT	GTC	ATG	654	
Phe	Ile	Phe 150	His	Lys	Gly	Ser	Tyr 155	Leu	Arg	Asn	Gly	Trp 160	Asn	Val	Met		
GAC	TTC	ATC	GTG	GTC	CTC	AGT	GGC	ATC	CTG	GCC	ACT	GCA	GGA	ACC	CAC	702	
Asp	Phe 165	Ile	Val	Val	Leu	Ser	Gly 170	Ile	Leu	Ala	Thr 175	Ala	Gly	Thr	His		
TTC	AAT	ACT	CAC	GTG	GAC	CTG	AGG	ACC	CTC	CGG	GCT	GTG	CGT	GTC	CTG	750	
Phe	Asn	Thr	His	Val	Asp 185	Leu	Arg	Thr	Leu	Arg	Ala	Val	Arg	Val	Leu 195		
180																	
CGG	CCT	TTG	AAG	CTC	GTG	TCA	GGG	ATA	CCT	AGC	CTG	CAG	ATT	GTG	TTG	798	
Arg	Pro	Leu	Lys	Leu 200	Val	Ser	Gly	Ile	Pro 205	Ser	Leu	Gln	Ile	Val	Leu 210		
AAG	TCC	ATC	ATG	AAG	GCC	ATG	GTA	CCT	CTT	CTG	CAG	ATT	GGC	CTT	CTG	846	
Lys	Ser	Ile	Met 215	Lys	Ala	Met	Val	Pro 220	Leu	Leu	Gln	Ile	Gly 225	Leu	Leu		
CTC	TTC	TTT	GCC	ATC	CTG	ATG	TTT	GCT	ATC	ATT	GGT	TTG	GAG	TTC	TAC	894	
Leu	Phe	Phe 230	Ala	Ile	Leu	Met	Phe 235	Ala	Ile	Ile	Gly	Leu 240	Glu	Phe	Tyr		
AGT	GGC	AAG	TTA	CAT	CGA	GCG	TGC	TTC	ATG	AAC	AAT	TCA	GGT	ATT	CTA	942	
Ser	Gly 245	Lys	Leu	His	Arg	Ala 250	Cys	Phe	Met	Asn	Asn 255	Ser	Gly	Ile	Leu		
GAA	GGA	TTT	GAC	CCC	CCT	CAC	CCA	TGT	GGT	GTG	CAG	GGC	TGC	CCA	GCT	990	
Glu	Gly	Phe	Asp	Pro	Pro 265	His	Pro	Cys	Gly	Val 270	Gln	Gly	Cys	Pro	Ala 275		
260																	
GGT	TAT	GAA	TGC	AAG	GAC	TGG	ATC	GGC	CCC	AAT	GAT	GGG	ATC	ACC	CAG	1038	
Gly	Tyr	Glu	Cys	Lys	Asp 280	Trp	Ile	Gly	Pro 285	Asn	Asp	Gly	Ile	Thr	Gln 290		
TTT	GAT	AAC	ATC	CTT	TTT	GCT	GTG	CTG	ACT	GTC	TTC	CAG	TGC	ATC	ACC	1086	
Phe	Asp	Asn	Ile	Leu	Phe	Ala	Val	Leu	Thr	Val	Phe	Gln	Cys	Ile	Thr 305		
295																	
ATG	GAA	GGG	TGG	ACC	ACT	GTG	CTG	TAC	AAT	ACC	AAT	GAT	GCC	TTA	GGA	1134	
Met	Glu	Gly 310	Trp	Thr	Thr	Val	Leu	Tyr	Asn	Thr	Asn	Asp	Ala	Leu	Gly		
310																	
GCC	ACC	TGG	AAT	TGG	CTG	TAC	TTC	ATC	CCC	CTC	ATC	ATC	ATT	GGA	TCC	1182	
Ala	Thr	Trp	Asn	Trp	Leu	Tyr 330	Phe	Ile	Pro	Leu	Ile 335	Ile	Ile	Gly	Ser		
325																	
TTC	TTT	GTT	CTC	AAC	CTA	GTC	CTG	GGA	GTG	CTT	TCC	GGG	GAA	TTT	GCC	1230	
Phe	Phe	Val	Leu	Asn	Leu 345	Val	Leu	Gly	Val	Leu	Ser	Gly	Glu	Phe	Ala 355		
340																	
AAA	GAG	AGA	GAG	AGA	GTG	GAG	AAC	CGA	AGG	GCT	TTC	ATG	AAG	CTG	CGG	1278	

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Lys	Glu	Arg	Glu	Arg	Val	Glu	Asn	Arg	Arg	Ala	Phe	Met	Lys	Leu	Arg	
				360					365					370		
CGC	CAG	CAG	CAG	ATT	GAG	CGT	GAG	CTG	AAT	GGC	TAC	CGT	GCC	TGG	ATA	1326
Arg	Gln	Gln	Gln	Ile	Glu	Arg	Glu	Leu	Asn	Gly	Tyr	Arg	Ala	Trp	Ile	
			375					380					385			
GAC	AAA	GCA	GAG	GAA	GTC	ATG	CTC	GCT	GAA	GAA	AAT	AAA	AAT	GCT	GGA	1374
Asp	Lys	Ala	Glu	Glu	Val	Met	Leu	Ala	Glu	Glu	Asn	Lys	Asn	Ala	Gly	
		390					395					400				
ACA	TCC	GCC	TTA	GAA	GTG	CTT	CGA	AGG	GCA	ACC	ATC	AAG	AGG	AGC	CGG	1422
Thr	Ser	Ala	Leu	Glu	Val	Leu	Arg	Arg	Ala	Thr	Ile	Lys	Arg	Ser	Arg	
	405					410					415					
ACA	GAG	GCC	ATG	ACT	CGA	GAC	TCC	AGT	GAT	GAG	CAC	TGT	GTT	GAT	ATC	1470
Thr	Glu	Ala	Met	Thr	Arg	Asp	Ser	Ser	Asp	Glu	His	Cys	Val	Asp	Ile	
420					425					430					435	
TCC	TCT	GTG	GGC	ACA	CCT	CTG	GCC	CGA	GCC	AGT	ATC	AAA	AGT	GCA	AAG	1518
Ser	Ser	Val	Gly	Thr	Pro	Leu	Ala	Arg	Ala	Ser	Ile	Lys	Ser	Ala	Lys	
				440					445					450		
GTA	GAC	GGG	GTC	TCT	TAT	TTC	CGG	CAC	AAG	GAA	AGG	CTT	CTG	CGC	ATC	1566
Val	Asp	Gly	Val	Ser	Tyr	Phe	Arg	His	Lys	Glu	Arg	Leu	Leu	Arg	Ile	
			455					460					465			
TCC	ATT	CGC	CAC	ATG	GTT	AAA	TCC	CAG	GTG	TTT	TAC	TGG	ATT	GTG	CTG	1614
Ser	Ile	Arg	His	Met	Val	Lys	Ser	Gln	Val	Phe	Tyr	Trp	Ile	Val	Leu	
	470						475					480				
AGC	CTT	GTG	GCA	CTC	AAC	ACT	GCC	TGT	GTG	GCC	ATT	GTC	CAT	CAC	AAC	1662
Ser	Leu	Val	Ala	Leu	Asn	Thr	Ala	Cys	Val	Ala	Ile	Val	His	His	Asn	
	485					490					495					
CAG	CCC	CAG	TGG	CTC	ACC	CAC	CTC	CTC	TAC	TAT	GCA	GAA	TTT	CTG	TTT	1710
Gln	Pro	Gln	Trp	Leu	Thr	His	Leu	Leu	Tyr	Tyr	Ala	Glu	Phe	Leu	Phe	
500					505					510					515	
CTG	GGA	CTC	TTC	CTC	TTG	GAG	ATG	TCC	CTG	AAG	ATG	TAT	GGC	ATG	GGG	1758
Leu	Gly	Leu	Phe	Leu	Leu	Glu	Met	Ser	Leu	Lys	Met	Tyr	Gly	Met	Gly	
				520					525					530		
CCT	CGC	CTT	TAT	TTT	CAC	TCT	TCA	TTC	AAC	TGC	TTT	GAT	TTT	GGG	GTC	1806
Pro	Arg	Leu	Tyr	Phe	His	Ser	Ser	Phe	Asn	Cys	Phe	Asp	Phe	Gly	Val	
			535					540					545			
ACA	GTG	GGC	AGT	ATC	TTT	GAA	GTG	GTC	TGG	GCA	ATC	TTC	AGA	CCT	GGT	1854
Thr	Val	Gly	Ser	Ile	Phe	Glu	Val	Val	Trp	Ala	Ile	Phe	Arg	Pro	Gly	
		550					555					560				
ACG	TCT	TTT	GGA	ATC	AGT	GTC	TTG	CGA	GCC	CTC	CGG	CTT	CTA	AGA	ATA	1902
Thr	Ser	Phe	Gly	Ile	Ser	Val	Leu	Arg	Ala	Leu	Arg	Leu	Leu	Arg	Ile	
	565					570					575					
TTT	AAA	ATA	ACC	AAG	TAT	TGG	GCT	TCC	CTA	CGG	AAT	TTG	GTG	GTC	TCC	1950

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Phe 580	Lys	Ile	Thr	Lys	Tyr 585	Trp	Ala	Ser	Leu	Arg 590	Asn	Leu	Val	Val	Ser 595	
TTG	ATG	AGC	TCA	ATG	AAG	TCT	ATC	ATC	AGT	TTG	CTT	TTC	CTC	CTC	TTC	1998
Leu	Met	Ser	Ser	Met	Lys	Ser	Ile	Ile	Ser	Leu	Leu	Phe	Leu	Leu	Phe	
				600					605					610		
CTC	TTC	ATC	GTT	GTC	TTT	GCT	CTC	CTA	GGA	ATG	CAG	TTA	TTT	GGA	GGC	2046
Leu	Phe	Ile	Val	Val	Phe	Ala	Leu	Leu	Gly	Met	Gln	Leu	Phe	Gly	Gly	
			615					620					625			
AGG	TTT	AAC	TTT	AAT	GAT	GGG	ACT	CCT	TCG	GCA	AAT	TTT	GAT	ACC	TTC	2094
Arg	Phe	Asn	Phe	Asn	Asp	Gly	Thr	Pro	Ser	Ala	Asn	Phe	Asp	Thr	Phe	
		630					635					640				
CCT	GCA	GCC	ATC	ATG	ACT	GTG	TTC	CAG	ATC	CTG	ACG	GGT	GAG	GAC	TGG	2142
Pro	Ala	Ala	Ile	Met	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gly	Glu	Asp	Trp	
		645				650					655					
AAT	GAG	GTG	ATG	TAC	AAT	GGG	ATC	CGC	TCC	CAG	GGT	GGG	GTC	AGC	TCA	2190
Asn	Glu	Val	Met	Tyr	Asn	Gly	Ile	Arg	Ser	Gln	Gly	Gly	Val	Ser	Ser	
660					665					670					675	
GGC	ATG	TGG	TCT	GCC	ATC	TAC	TTC	ATT	GTG	CTC	ACC	TTG	TTT	GGC	AAC	2238
Gly	Met	Trp	Ser	Ala	Ile	Tyr	Phe	Ile	Val	Leu	Thr	Leu	Phe	Gly	Asn	
				680					685					690		
TAC	ACG	CTA	CTG	AAT	GTG	TTC	TTG	GCT	ATC	GCT	GTG	GAT	AAT	CTC	GCC	2286
Tyr	Thr	Leu	Leu	Asn	Val	Phe	Leu	Ala	Ile	Ala	Val	Asp	Asn	Leu	Ala	
				695				700					705			
AAC	GCC	CAG	GAA	CTG	ACC	AAG	GAT	GAA	CAG	GAG	GAA	GAA	GAG	GCC	TTC	2334
Asn	Ala	Gln	Glu	Leu	Thr	Lys	Asp	Glu	Gln	Glu	Glu	Glu	Glu	Ala	Phe	
		710					715					720				
AAC	CAG	AAA	CAT	GCA	CTG	CAG	AAG	GCC	AAG	GAG	GTC	AGC	CCG	ATG	TCT	2382
Asn	Gln	Lys	His	Ala	Leu	Gln	Lys	Ala	Lys	Glu	Val	Ser	Pro	Met	Ser	
		725				730					735					
GCA	CCC	AAC	ATG	CCT	TCG	ATC	GAA	AGA	GAC	AGA	AGG	AGA	AGA	CAC	CAC	2430
Ala	Pro	Asn	Met	Pro	Ser	Ile	Glu	Arg	Asp	Arg	Arg	Arg	Arg	His	His	
					745					750				755		
ATG	TCG	ATG	TGG	GAG	CCA	CGC	AGC	AGC	CAC	CTG	AGG	GAG	CGG	AGG	CGC	2478
Met	Ser	Met	Trp	Glu	Pro	Arg	Ser	Ser	His	Leu	Arg	Glu	Arg	Arg	Arg	
				760					765					770		
CGG	CAC	CAC	ATG	TCC	GTG	TGG	GAG	CAG	CGT	ACC	AGC	CAG	CTG	AGG	AAG	2526
Arg	His	His	Met	Ser	Val	Trp	Glu	Gln	Arg	Thr	Ser	Gln	Leu	Arg	Lys	
			775					780					785			
CAC	ATG	CAG	ATG	TCC	AGC	CAG	GAG	GCC	CTC	AAC	AGA	GAG	GAG	GCG	CCG	2574
His	Met	Gln	Met	Ser	Ser	Gln	Glu	Ala	Leu	Asn	Arg	Glu	Glu	Ala	Pro	
		790					795					800				
ACC	ATG	AAC	CCG	CTC	AAC	CCC	CTC	AAC	CCG	CTC	AGC	TCC	CTC	AAC	CCG	2622

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Thr	Met	Asn	Pro	Leu	Asn	Pro	Leu	Asn	Pro	Leu	Ser	Ser	Leu	Asn	Pro	
	805					810					815					
CTC	AAT	GCC	CAC	CCC	AGC	CTT	TAT	CGG	CGA	CCC	AGG	GCC	ATT	GAG	GGC	2670
Leu	Asn	Ala	His	Pro	Ser	Leu	Tyr	Arg	Arg	Pro	Arg	Ala	Ile	Glu	Gly	
820					825					830					835	
CTG	GCC	CTG	GGC	CTG	GCC	CTG	GAG	AAG	TTC	GAG	GAG	GAG	CGC	ATC	AGC	2718
Leu	Ala	Leu	Gly	Leu	Ala	Leu	Glu	Lys	Phe	Glu	Glu	Glu	Arg	Ile	Ser	
				840					845					850		
CGT	GGG	GGG	TCC	CTC	AAG	GGG	GAT	GGA	GGG	GAC	CGA	TCC	AGT	GCC	CTG	2766
Arg	Gly	Gly	Ser	Leu	Lys	Gly	Asp	Gly	Gly	Asp	Arg	Ser	Ser	Ala	Leu	
			855					860					865			
GAC	AAC	CAG	AGG	ACC	CCT	TTG	TCC	CTG	GGC	CAG	CGG	GAG	CCA	CCA	TGG	2814
Asp	Asn	Gln	Arg	Thr	Pro	Leu	Ser	Leu	Gly	Gln	Arg	Glu	Pro	Pro	Trp	
		870					875					880				
CTG	GCC	AGG	CCC	TGT	CAT	GGA	AAC	TGT	GAC	CCG	ACT	CAG	CAG	GAG	GCA	2862
Leu	Ala	Arg	Pro	Cys	His	Gly	Asn	Cys	Asp	Pro	Thr	Gln	Gln	Glu	Ala	
	885					890					895					
GGG	GGA	GGA	GAG	GCT	GTG	GTG	ACC	TTT	GAG	GAC	CGG	GCC	AGG	CAC	AGG	2910
Gly	Gly	Gly	Glu	Ala	Val	Val	Thr	Phe	Glu	Asp	Arg	Ala	Arg	His	Arg	
900					905					910					915	
CAG	AGC	CAA	CGG	CGC	AGC	CGG	CAT	CGC	CGC	GTC	AGG	ACA	GAA	GGC	AAG	2958
Gln	Ser	Gln	Arg	Arg	Ser	Arg	His	Arg	Arg	Val	Arg	Thr	Glu	Gly	Lys	
				920					925					930		
GAG	TCC	TCT	TCA	GCC	TCC	CGG	AGC	AGG	TCT	GCC	AGC	CAG	GAA	CGC	AGT	3006
Glu	Ser	Ser	Ser	Ala	Ser	Arg	Ser	Arg	Ser	Ala	Ser	Gln	Glu	Arg	Ser	
			935					940					945			
CTG	GAT	GAA	GCC	ATG	CCC	ACT	GAA	GGG	GAG	AAG	GAC	CAT	GAG	CTC	AGG	3054
Leu	Asp	Glu	Ala	Met	Pro	Thr	Glu	Gly	Glu	Lys	Asp	His	Glu	Leu	Arg	
		950					955					960				
GGC	AAC	CAT	GGT	GCC	AAG	GAG	CCA	ACG	ATC	CAA	GAA	GAG	AGA	GCC	CAG	3102
Gly	Asn	His	Gly	Ala	Lys	Glu	Pro	Thr	Ile	Gln	Glu	Glu	Arg	Ala	Gln	
	965					970					975					
GAT	TTA	AGG	AGG	ACC	AAC	AGT	CTG	ATG	GTG	TCC	AGA	GGC	TCC	GGG	CTG	3150
Asp	Leu	Arg	Arg	Thr	Asn	Ser	Leu	Met	Val	Ser	Arg	Gly	Ser	Gly	Leu	
980					985					990					995	
GCA	GGA	GGC	CTT	GAT	GAG	GCT	GAC	ACC	CCC	CTA	GTC	CTG	CCC	CAT	CCT	3198
Ala	Gly	Gly	Leu	Asp	Glu	Ala	Asp	Thr	Pro	Leu	Val	Leu	Pro	His	Pro	
				1000					1005					1010		
GAG	CTG	GAA	GTG	GGG	AAG	CAC	GTG	GTG	CTG	ACG	GAG	CAG	GAG	CCA	GAA	3246
Glu	Leu	Glu	Val	Gly	Lys	His	Val	Val	Leu	Thr	Glu	Gln	Glu	Pro	Glu	
			1015					1020					1025			
GGC	AGC	AGT	GAG	CAG	GCC	CTG	CTG	GGG	AAT	GTG	CAG	CTA	GAC	ATG	GGC	3294

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Gly	Ser	Ser	Glu	Gln	Ala	Leu	Leu	Gly	Asn	Val	Gln	Leu	Asp	Met	Gly		
		1030					1035					1040					
CGG	GTC	ATC	AGC	CAG	AGC	GAG	CCT	GAC	CTC	TCC	TGC	ATC	ACG	GCC	AAC	3342	
Arg	Val	Ile	Ser	Gln	Ser	Glu	Pro	Asp	Leu	Ser	Cys	Ile	Thr	Ala	Asn		
		1045				1050					1055						
ACG	GAC	AAG	GCC	ACC	ACC	GAG	AGC	ACC	AGC	GTC	ACC	GTC	GCC	ATC	CCC	3390	
Thr	Asp	Lys	Ala	Thr	Thr	Glu	Ser	Thr	Ser	Val	Thr	Val	Ala	Ile	Pro		
1060						1065				1070					1075		
GAC	GTG	GAC	CCC	TTG	GTG	GAC	TCA	ACC	GTG	GTG	CAC	ATT	AGC	AAC	AAG	3438	
Asp	Val	Asp	Pro	Leu	Val	Asp	Ser	Thr	Val	Val	His	Ile	Ser	Asn	Lys		
				1080					1085					1090			
ACG	GAT	GGG	GAA	GCC	AGT	CCC	TTG	AAG	GAG	GCA	GAG	ATC	AGA	GAG	GAT	3486	
Thr	Asp	Gly	Glu	Ala	Ser	Pro	Leu	Lys	Glu	Ala	Glu	Ile	Arg	Glu	Asp		
			1095					1100					1105				
GAG	GAG	GAG	GTG	GAG	AAG	AAG	AAG	CAG	AAG	AAG	GAG	AAG	CGT	GAG	ACA	3534	
Glu	Glu	Glu	Val	Glu	Lys	Lys	Lys	Gln	Lys	Lys	Glu	Lys	Arg	Glu	Thr		
		1110					1115					1120					
GGC	AAA	GCC	ATG	GTG	CCC	CAC	AGC	TCA	ATG	TTC	ATC	TTC	AGC	ACC	ACC	3582	
Gly	Lys	Ala	Met	Val	Pro	His	Ser	Ser	Met	Phe	Ile	Phe	Ser	Thr	Thr		
	1125					1130					1135						
AAC	CCG	ATC	CGG	AGG	GCC	TGC	CAC	TAC	ATC	GTG	AAC	CTG	CGC	TAC	TTT	3630	
Asn	Pro	Ile	Arg	Arg	Ala	Cys	His	Tyr	Ile	Val	Asn	Leu	Arg	Tyr	Phe		
1140					1145				1150						1155		
GAG	ATG	TGC	ATC	CTC	CTG	GTG	ATT	GCA	GCC	AGC	AGC	ATC	GCC	CTG	GCG	3678	
Glu	Met	Cys	Ile	Leu	Leu	Val	Ile	Ala	Ala	Ser	Ser	Ile	Ala	Leu	Ala		
				1160					1165					1170			
GCA	GAG	GAC	CCC	GTC	CTG	ACC	AAC	TCG	GAG	CGC	AAC	AAA	GTC	CTG	AGG	3726	
Ala	Glu	Asp	Pro	Val	Leu	Thr	Asn	Ser	Glu	Arg	Asn	Lys	Val	Leu	Arg		
			1175					1180					1185				
TAT	TTT	GAC	TAT	GTG	TTC	ACG	GGC	GTG	TTC	ACC	TTT	GAG	ATG	GTT	ATA	3774	
Tyr	Phe	Asp	Tyr	Val	Phe	Thr	Gly	Val	Phe	Thr	Phe	Glu	Met	Val	Ile		
		1190					1195					1200					
AAG	ATG	ATA	GAC	CAA	GGC	TTG	ATC	CTG	CAG	GAT	GGG	TCC	TAC	TTC	CGA	3822	
Lys	Met	Ile	Asp	Gln	Gly	Leu	Ile	Leu	Gln	Asp	Gly	Ser	Tyr	Phe	Arg		
	1205					1210					1215						
GAC	TTG	TGG	AAC	ATC	CTG	GAC	TTT	GTG	GTG	GTC	GTT	GGC	GCA	TTG	GTG	3870	
Asp	Leu	Trp	Asn	Ile	Leu	Asp	Phe	Val	Val	Val	Val	Gly	Ala	Leu	Val		
1220					1225					1230					1235		
GCC	TTT	GCT	CTG	GCG	AAC	GCT	TTG	GGA	ACC	AAC	AAA	GGA	CGG	GAC	ATC	3918	
Ala	Phe	Ala	Leu	Ala	Asn	Ala	Leu	Gly	Thr	Asn	Lys	Gly	Arg	Asp	Ile		
				1240				1245						1250			
AAG	ACC	ATC	AAG	TCT	CTG	CGG	GTG	CTC	CGA	GTT	CTA	AGG	CCA	CTG	AAA	3966	

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Lys	Thr	Ile	Lys	Ser	Leu	Arg	Val	Leu	Arg	Val	Leu	Arg	Pro	Leu	Lys	
			1255					1260					1265			
ACC	ATC	AAG	CGC	TTG	CCC	AAG	CTC	AAG	GCC	GTC	TTC	GAC	TGC	GTA	GTG	4014
Thr	Ile	Lys	Arg	Leu	Pro	Lys	Leu	Lys	Ala	Val	Phe	Asp	Cys	Val	Val	
		1270					1275					1280				
ACC	TCC	TTG	AAG	AAT	GTC	TTC	AAC	ATA	CTC	ATT	GTG	TAC	AAG	CTC	TTC	4062
Thr	Ser	Leu	Lys	Asn	Val	Phe	Asn	Ile	Leu	Ile	Val	Tyr	Lys	Leu	Phe	
	1285					1290					1295					
ATG	TTC	ATC	TTT	GCT	GTC	ATC	GCA	GTT	CAG	CTC	TTC	AAG	GGA	AAG	TTC	4110
Met	Phe	Ile	Phe	Ala	Val	Ile	Ala	Val	Gln	Leu	Phe	Lys	Gly	Lys	Phe	
1300					1305					1310					1315	
TTT	TAT	TGC	ACG	GAC	AGT	TCC	AAG	GAC	ACA	GAG	AAG	GAG	TGC	ATA	GGC	4158
Phe	Tyr	Cys	Thr	Asp	Ser	Ser	Lys	Asp	Thr	Glu	Lys	Glu	Cys	Ile	Gly	
				1320					1325					1330		
AAC	TAT	GTA	GAT	CAC	GAG	AAA	AAC	AAG	ATG	GAG	GTG	AAG	GGC	CGG	GAA	4206
Asn	Tyr	Val	Asp	His	Glu	Lys	Asn	Lys	Met	Glu	Val	Lys	Gly	Arg	Glu	
			1335					1340					1345			
TGG	AAG	CGC	CAT	GAA	TTC	CAC	TAC	GAC	AAC	ATT	ATC	TGG	GCC	CTG	CTG	4254
Trp	Lys	Arg	His	Glu	Phe	His	Tyr	Asp	Asn	Ile	Ile	Trp	Ala	Leu	Leu	
		1350					1355					1360				
ACC	CTC	TTC	ACC	GTC	TCC	ACA	GGG	GAA	GGA	TGG	CCT	CAA	GTT	CTG	CAG	4302
Thr	Leu	Phe	Thr	Val	Ser	Thr	Gly	Glu	Gly	Trp	Pro	Gln	Val	Leu	Gln	
	1365					1370					1375					
CAC	TCT	GTA	GAT	GTG	ACA	GAG	GAA	GAC	CGA	GGC	CCA	AGC	CGC	AGC	AAC	4350
His	Ser	Val	Asp	Val	Thr	Glu	Glu	Asp	Arg	Gly	Pro	Ser	Arg	Ser	Asn	
1380					1385					1390					1395	
CGC	ATG	GAG	ATG	TCT	ATC	TTT	TAT	GTA	GTC	TAC	TTT	GTG	GTC	TTC	CCC	4398
Arg	Met	Glu	Met	Ser	Ile	Phe	Tyr	Val	Val	Tyr	Phe	Val	Val	Phe	Pro	
				1400					1405					1410		
TTC	TTC	TTT	GTC	AAT	ATC	TTT	GTG	GCT	CTC	ATC	ATC	ATC	ACC	TTC	CAG	4446
Phe	Phe	Phe	Val	Asn	Ile	Phe	Val	Ala	Leu	Ile	Ile	Ile	Thr	Phe	Gln	
			1415					1420					1425			
GAG	CAA	GGG	GAT	AAG	ATG	ATG	GAG	GAG	TGC	AGC	CTG	GAG	AAG	AAT	GAG	4494
Glu	Gln	Gly	Asp	Lys	Met	Met	Glu	Glu	Cys	Ser	Leu	Glu	Lys	Asn	Glu	
		1430					1435					1440				
AGG	GCG	TGC	ATC	GAC	TTC	GCC	ATC	AGC	GCC	AAA	CCT	CTC	ACC	CGC	TAC	4542
Arg	Ala	Cys	Ile	Asp	Phe	Ala	Ile	Ser	Ala	Lys	Pro	Leu	Thr	Arg	Tyr	
	1445					1450					1455					
ATG	CCG	CAG	AAC	AGA	CAC	ACC	TTC	CAG	TAC	CGC	GTG	TGG	CAC	TTT	GTG	4590
Met	Pro	Gln	Asn	Arg	His	Thr	Phe	Gln	Tyr	Arg	Val	Trp	His	Phe	Val	
1460					1465					1470					1475	
GTG	TCT	CCG	TCC	TTT	GAG	TAC	ACC	ATT	ATG	GCC	ATG	ATC	GCC	TTG	AAT	4638

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Val	Ser	Pro	Ser	Phe	Glu	Tyr	Thr	Ile	Met	Ala	Met	Ile	Ala	Leu	Asn	
				1480					1485					1490		
ACT	GTT	GTG	CTG	ATG	ATG	AAG	TAT	TAT	TCT	GCT	CCC	TGT	ACC	TAT	GAG	4686
Thr	Val	Val	Leu	Met	Met	Lys	Tyr	Tyr	Ser	Ala	Pro	Cys	Thr	Tyr	Glu	
			1495					1500					1505			
CTG	GCC	CTG	AAG	TAC	CTG	AAT	ATC	GCC	TTC	ACC	ATG	GTG	TTT	TCC	CTG	4734
Leu	Ala	Leu	Lys	Tyr	Leu	Asn	Ile	Ala	Phe	Thr	Met	Val	Phe	Ser	Leu	
			1510				1515					1520				
GAA	TGT	GTC	CTG	AAG	GTC	ATC	GCT	TTT	GGC	TTT	TTG	AAC	TAT	TTC	CGA	4782
Glu	Cys	Val	Leu	Lys	Val	Ile	Ala	Phe	Gly	Phe	Leu	Asn	Tyr	Phe	Arg	
	1525					1530					1535					
GAC	ACC	TGG	AAT	ATC	TTT	GAC	TTC	ATC	ACC	GTG	ATT	GGC	AGT	ATC	ACA	4830
Asp	Thr	Trp	Asn	Ile	Phe	Asp	Phe	Ile	Thr	Val	Ile	Gly	Ser	Ile	Thr	
1540					1545					1550					1555	
GAA	ATT	ATC	CTG	ACA	GAC	AGC	AAG	CTG	GTG	AAC	ACC	AGT	GGC	TTC	AAT	4878
Glu	Ile	Ile	Leu	Thr	Asp	Ser	Lys	Leu	Val	Asn	Thr	Ser	Gly	Phe	Asn	
				1560					1565					1570		
ATG	AGC	TTT	CTG	AAG	CTC	TTC	CGA	GCT	GCC	CGC	CTC	ATA	AAG	CTC	CTG	4926
Met	Ser	Phe	Leu	Lys	Leu	Phe	Arg	Ala	Ala	Arg	Leu	Ile	Lys	Leu	Leu	
			1575					1580					1585			
CGT	CAG	GGC	TAT	ACC	ATA	CGC	ATT	TTG	CTG	TGG	ACC	TTT	GTG	CAG	TCC	4974
Arg	Gln	Gly	Tyr	Thr	Ile	Arg	Ile	Leu	Leu	Trp	Thr	Phe	Val	Gln	Ser	
		1590					1595					1600				
TTT	AAG	GCC	CTC	CCT	TAT	GTC	TGC	CTT	TTA	ATT	GCC	ATG	CTT	TTC	TTC	5022
Phe	Lys	Ala	Leu	Pro	Tyr	Val	Cys	Leu	Leu	Ile	Ala	Met	Leu	Phe	Phe	
	1605					1610					1615					
ATT	TAT	GCC	ATC	ATT	GGG	ATG	CAG	GTA	TTT	GGA	AAC	ATA	AAA	TTA	GAC	5070
Ile	Tyr	Ala	Ile	Ile	Gly	Met	Gln	Val	Phe	Gly	Asn	Ile	Lys	Leu	Asp	
1620					1625					1630					1635	
GAG	GAG	AGT	CAC	ATC	AAC	CGG	CAC	AAC	AAC	TTC	CGG	AGT	TTC	TTT	GGG	5118
Glu	Glu	Ser	His	Ile	Asn	Arg	His	Asn	Asn	Phe	Arg	Ser	Phe	Phe	Gly	
				1640					1645					1650		
TCC	CTA	ATG	CTA	CTC	TTC	AGG	AGT	GCC	ACA	GGT	GAG	GCC	TGG	CAG	GAG	5166
Ser	Leu	Met	Leu	Leu	Phe	Arg	Ser	Ala	Thr	Gly	Glu	Ala	Trp	Gln	Glu	
			1655					1660					1665			
ATT	ATG	CTG	TCA	TGC	CTT	GGG	GAG	AAG	GGC	TGT	GAG	CCT	GAC	ACC	ACC	5214
Ile	Met	Leu	Ser	Cys	Leu	Gly	Glu	Lys	Gly	Cys	Glu	Pro	Asp	Thr	Thr	
		1670				1675						1680				
GCA	CCA	TCA	GGG	CAG	AAC	GAG	AAT	GAA	CGC	TGC	GGC	ACC	GAT	CTG	GCC	5262
Ala	Pro	Ser	Gly	Gln	Asn	Glu	Asn	Glu	Arg	Cys	Gly	Thr	Asp	Leu	Ala	
	1685					1690					1695					
TAC	GTG	TAC	TTT	GTC	TCC	TTC	ATC	TTC	TTC	TGC	TCC	TTC	TTG	ATG	CTC	5310

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Tyr	Val	Tyr	Phe	Val	Ser	Phe	Ile	Phe	Phe	Cys	Ser	Phe	Leu	Met	Leu	
1700					1705					1710					1715	
AAC	CTG	TTT	GTG	GCC	GTC	ATC	ATG	GAC	AAC	TTT	GAG	TAC	CTG	ACT	CGG	5358
Asn	Leu	Phe	Val	Ala	Val	Ile	Met	Asp	Asn	Phe	Glu	Tyr	Leu	Thr	Arg	
				1720					1725					1730		
GAC	TCC	TCC	ATC	CTG	GGG	CCT	CAC	CAC	TTG	GAC	GAG	TTT	GTC	CGC	GTC	5406
Asp	Ser	Ser	Ile	Leu	Gly	Pro	His	His	Leu	Asp	Glu	Phe	Val	Arg	Val	
			1735					1740					1745			
TGG	GCA	GAA	TAT	GAC	CGA	GCA	GCA	TGT	GGC	CGC	ATC	CAT	TAC	ACT	GAG	5454
Trp	Ala	Glu	Tyr	Asp	Arg	Ala	Ala	Cys	Gly	Arg	Ile	His	Tyr	Thr	Glu	
		1750					1755					1760				
ATG	TAT	GAA	ATG	CTG	ACT	CTC	ATG	TCA	CCT	CCG	CTA	GGC	CTC	GGC	AAG	5502
Met	Tyr	Glu	Met	Leu	Thr	Leu	Met	Ser	Pro	Pro	Leu	Gly	Leu	Gly	Lys	
	1765					1770					1775					
AGA	TGT	CCC	TCC	AAA	GTG	GCA	TAT	AAG	AGG	TTG	GTC	CTG	ATG	AAC	ATG	5550
Arg	Cys	Pro	Ser	Lys	Val	Ala	Tyr	Lys	Arg	Leu	Val	Leu	Met	Asn	Met	
1780					1785					1790					1795	
CCA	GTA	GCT	GAG	GAC	ATG	ACG	GTC	CAC	TTC	ACC	TCC	ACA	CTT	ATG	GCT	5598
Pro	Val	Ala	Glu	Asp	Met	Thr	Val	His	Phe	Thr	Ser	Thr	Leu	Met	Ala	
				1800					1805					1810		
CTG	ATC	CGG	ACA	GCT	CTG	GAC	ATT	AAA	ATT	GCC	AAA	GGT	GGT	GCA	GAC	5646
Leu	Ile	Arg	Thr	Ala	Leu	Asp	Ile	Lys	Ile	Ala	Lys	Gly	Gly	Ala	Asp	
			1815					1820					1825			
AGG	CAG	CAG	CTA	GAC	TCA	GAG	CTA	CAA	AAG	GAG	ACC	CTA	GCC	ATC	TGG	5694
Arg	Gln	Gln	Leu	Asp	Ser	Glu	Leu	Gln	Lys	Glu	Thr	Leu	Ala	Ile	Trp	
		1830					1835					1840				
CCT	CAC	CTA	TCC	CAG	AAG	ATG	CTG	GAT	CTG	CTT	GTG	CCC	ATG	CCC	AAA	5742
Pro	His	Leu	Ser	Gln	Lys	Met	Leu	Asp	Leu	Leu	Val	Pro	Met	Pro	Lys	
	1845					1850					1855					
GCC	TCT	GAC	CTG	ACT	GTG	GGC	AAA	ATC	TAT	GCA	GCA	ATG	ATG	ATC	ATG	5790
Ala	Ser	Asp	Leu	Thr	Val	Gly	Lys	Ile	Tyr	Ala	Ala	Met	Met	Ile	Met	
1860					1865					1870					1875	
GAC	TAC	TAT	AAG	CAG	AGT	AAG	GTG	AAG	AAG	CAG	AGG	CAG	CAG	CTG	GAG	5838
Asp	Tyr	Tyr	Lys	Gln	Ser	Lys	Val	Lys	Lys	Gln	Arg	Gln	Gln	Leu	Glu	
			1880						1885					1890		
GAA	CAG	AAA	AAT	GCC	CCC	ATG	TTC	CAG	CGC	ATG	GAG	CCT	TCA	TCT	CTG	5886
Glu	Gln	Lys	Asn	Ala	Pro	Met	Phe	Gln	Arg	Met	Glu	Pro	Ser	Ser	Leu	
			1895					1900					1905			
CCT	CAG	GAG	ATC	ATT	GCT	AAT	GCC	AAA	GCC	CTG	CCT	TAC	CTC	CAG	CAG	5934
Pro	Gln	Glu	Ile	Ala	Asn	Ala	Lys	Ala	Leu	Pro	Tyr	Leu	Gln	Gln		
		1910				1915						1920				
GAC	CCC	GTT	TCA	GGC	CTG	AGT	GGC	CGG	AGT	GGA	TAC	CCT	TCG	ATG	AGT	5982

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Asp	Pro	Val	Ser	Gly	Leu	Ser	Gly	Arg	Ser	Gly	Tyr	Pro	Ser	Met	Ser	
1925						1930					1935					
CCA	CTC	TCT	CCC	CAG	GAT	ATA	TTC	CAG	TTG	GCT	TGT	ATG	GAC	CCC	GCC	6030
Pro	Leu	Ser	Pro	Gln	Asp	Ile	Phe	Gln	Leu	Ala	Cys	Met	Asp	Pro	Ala	
1940					1945					1950					1955	
GAT	GAC	GGA	CAG	TTC	CAA	GAA	CGG	CAG	TCT	CTG	GTG	GTG	ACA	GAC	CCT	6078
Asp	Asp	Gly	Gln	Phe	Gln	Glu	Arg	Gln	Ser	Leu	Val	Val	Thr	Asp	Pro	
				1960					1965					1970		
AGC	TCC	ATG	AGA	CGT	TCA	TTT	TCC	ACT	ATT	CGG	GAT	AAG	CGT	TCA	AAT	6126
Ser	Ser	Met	Arg	Arg	Ser	Phe	Ser	Thr	Ile	Arg	Asp	Lys	Arg	Ser	Asn	
			1975					1980					1985			
TCC	TCG	TGG	TTG	GAG	GAA	TTC	TCC	ATG	GAG	CGA	AGC	AGT	GAA	AAT	ACC	6174
Ser	Ser	Trp	Leu	Glu	Glu	Phe	Ser	Met	Glu	Arg	Ser	Ser	Glu	Asn	Thr	
		1990					1995					2000				
TAC	AAG	TCC	CGT	CGC	CGG	AGT	TAC	CAC	TCC	TCC	TTG	CGG	CTG	TCA	GCC	6222
Tyr	Lys	Ser	Arg	Arg	Arg	Ser	Tyr	His	Ser	Ser	Leu	Arg	Leu	Ser	Ala	
	2005					2010					2015					
CAC	CGC	CTG	AAC	TCT	GAT	TCA	GGC	CAC	AAG	TCT	GAC	ACT	CAC	CCC	TCA	6270
His	Arg	Leu	Asn	Ser	Asp	Ser	Gly	His	Lys	Ser	Asp	Thr	His	Pro	Ser	
2020					2025					2030					2035	
GGG	GGC	AGG	GAG	CGG	CGA	CGA	TCA	AAA	GAG	CGA	AAG	CAT	CTT	CTC	TCT	6318
Gly	Gly	Arg	Glu	Arg	Arg	Arg	Ser	Lys	Glu	Arg	Lys	His	Leu	Leu	Ser	
				2040					2045					2050		
CCT	GAT	GTC	TCC	CGC	TGC	AAT	TCA	GAA	GAG	CGA	GGG	ACC	CAG	GCT	GAC	6366
Pro	Asp	Val	Ser	Arg	Cys	Asn	Ser	Glu	Glu	Arg	Gly	Thr	Gln	Ala	Asp	
			2055					2060					2065			
TGG	GAG	TCC	CCA	GAG	CGC	CGT	CAA	TCC	AGG	TCA	CCC	AGT	GAG	GGC	AGG	6414
Trp	Glu	Ser	Pro	Glu	Arg	Arg	Gln	Ser	Arg	Ser	Pro	Ser	Glu	Gly	Arg	
		2070					2075					2080				
TCA	CAG	ACG	CCC	AAC	AGA	CAG	GGC	ACA	GGT	TCC	CTA	AGT	GAG	AGC	TCC	6462
Ser	Gln	Thr	Pro	Asn	Arg	Gln	Gly	Thr	Gly	Ser	Leu	Ser	Glu	Ser	Ser	
	2085					2090					2095					
ATC	CCC	TCT	GTC	TCT	GAC	ACC	AGC	ACC	CCA	AGA	AGA	AGT	CGT	CGG	CAG	6510
Ile	Pro	Ser	Val	Ser	Asp	Thr	Ser	Thr	Pro	Arg	Arg	Ser	Arg	Arg	Gln	
2100					2105					2110					2115	
CTC	CCA	CCC	GTC	CCG	CCA	AAG	CCC	CGG	CCC	CTC	CTT	TCC	TAC	AGC	TCC	6558
Leu	Pro	Pro	Val	Pro	Pro	Lys	Pro	Arg	Pro	Leu	Leu	Ser	Tyr	Ser	Ser	
				2120					2125					2130		
CTG	ATT	CGA	CAC	GCG	GGC	AGC	ATC	TCT	CCA	CCT	GCT	GAT	GGA	AGC	GAG	6606
Leu	Ile	Arg	His	Ala	Gly	Ser	Ile	Ser	Pro	Pro	Ala	Asp	Gly	Ser	Glu	
			2135					2140				2145				
GAG	GGC	TCC	CCG	CTG	ACC	TCC	CAA	GCT	CTG	GAG	AGC	AAC	AAT	GCT	TGG	6654

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Glu Gly Ser Pro Leu Thr Ser Gln Ala Leu Glu Ser Asn Asn Ala Trp	
2150 2155 2160	
CTG ACC GAG TCT TCC AAC TCT CCG CAC CCC CAG CAG AGG CAA CAT GCC	6702
Leu Thr Glu Ser Ser Asn Ser Pro His Pro Gln Gln Arg Gln His Ala	
2165 2170 2175	
TCC CCA CAG CGC TAC ATC TCC GAG CCC TAC TTG GCC CTG CAC GAA GAC	6750
Ser Pro Gln Arg Tyr Ile Ser Glu Pro Tyr Leu Ala Leu His Glu Asp	
2180 2185 2190 2195	
TCC CAC GCC TCA GAC TGT GTT GAG GAG GAG ACG CTC ACT TTC GAA GCA	6798
Ser His Ala Ser Asp Cys Val Glu Glu Glu Thr Leu Thr Phe Glu Ala	
2200 2205 2210	
GCC GTG GCT ACT AGC CTG GGC CGT TCC AAC ACC ATC GGC TCA GCC CCA	6846
Ala Val Ala Thr Ser Leu Gly Arg Ser Asn Thr Ile Gly Ser Ala Pro	
2215 2220 2225	
CCC CTG CGG CAT AGC TGG CAG ATG CCC AAC GGG CAC TAT CGG CGG CGG	6894
Pro Leu Arg His Ser Trp Gln Met Pro Asn Gly His Tyr Arg Arg Arg	
2230 2235 2240	
AGG CGC GGG GGG CCT GGG CCA GGC ATG ATG TGT GGG GCT GTC AAC AAC	6942
Arg Arg Gly Gly Pro Gly Pro Gly Met Met Cys Gly Ala Val Asn Asn	
2245 2250 2255	
CTG CTA AGT GAC ACG GAA GAA GAT GAC AAA TGC TAGAGGCTGC TCCCCCTCC	6995
Leu Leu Ser Asp Thr Glu Glu Asp Asp Lys Cys	
2260 2265 2270	
GATGCATGCT CTTCTCTCAC ATGGAGAAAA CCAAGACAGA ATTGGGAAGC CAGTGCGGCC	7055
CCGCGGGGAG GAAGAGGGAA AAGGAAGATG GAAG	7089

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2634 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1983
- (D) OTHER INFORMATION: /standard_name= "Beta-2d"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

ATG GTC CAA AGG GAC ATG TCC AAG TCT CCT CCC ACA CCG GCG GCG GCG	48
Met Val Gln Arg Asp Met Ser Lys Ser Pro Pro Thr Pro Ala Ala Ala	

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1	5	10	15	
GTG GCG CAG GAG ATC CAG ATG GAA CTG CTA GAG AAC GTG GCT CCC GCG				96
Val Ala Gln Glu Ile Gln Met Glu Leu Leu Glu Asn Val Ala Pro Ala	20	25	30	
GGG GCG CTC GGA GCC GCC GCA CAG TCA TAT GGA AAA GGA GCC AGA AGG				144
Gly Ala Leu Gly Ala Ala Ala Gln Ser Tyr Gly Lys Gly Ala Arg Arg	35	40	45	
AAA AAC AGA TTT AAA GGA TCT GAT GGA AGC ACG TCA TCT GAT ACT ACC				192
Lys Asn Arg Phe Lys Gly Ser Asp Gly Ser Thr Ser Asp Thr Thr	50	55	60	
TCA AAT AGT TTT GTT CGC CAG GGT TCG GCA GAC TCC TAC ACT AGC CGT				240
Ser Asn Ser Phe Val Arg Gln Gly Ser Ala Asp Ser Tyr Thr Ser Arg	65	70	75	80
CCA TCC GAT TCC GAT GTA TCT CTG GAG GAG GAC CGG GAG GCA GTG CGC				288
Pro Ser Asp Ser Asp Val Ser Leu Glu Glu Asp Arg Glu Ala Val Arg	85	90	95	
AGA GAA GCG GAG CGG CAG GCC CAG GCA CAG TTG GAA AAA GCA AAG ACA				336
Arg Glu Ala Glu Arg Gln Ala Gln Ala Gln Leu Glu Lys Ala Lys Thr	100	105	110	
AAG CCC GTT GCA TTT GCG GTT CGG ACA AAT GTC AGC TAC AGT GCG GCC				384
Lys Pro Val Ala Phe Ala Val Arg Thr Asn Val Ser Tyr Ser Ala Ala	115	120	125	
CAT GAA GAT GAT GTT CCA GTG CCT GGC ATG GCC ATC TCA TTC GAA GCA				432
His Glu Asp Asp Val Pro Val Pro Gly Met Ala Ile Ser Phe Glu Ala	130	135	140	
AAA GAT TTT CTG CAT GTT AAG GAA AAA TTT AAC AAT GAC TGG TGG ATA				480
Lys Asp Phe Leu His Val Lys Glu Lys Phe Asn Asn Asp Trp Trp Ile	145	150	155	160
GGG CGA TTG GTA AAA GAA GGC TGT GAA ATC GGA TTC ATT CCA AGC CCA				528
Gly Arg Leu Val Lys Glu Gly Cys Glu Ile Gly Phe Ile Pro Ser Pro	165	170	175	
GTC AAA CTA GAA AAC ATG AGG CTG CAG CAT GAA CAG AGA GCC AAG CAA				576
Val Lys Leu Glu Asn Met Arg Leu Gln His Glu Gln Arg Ala Lys Gln	180	185	190	
GGG AAA TTC TAC TCC AGT AAA TCA GGA GGA AAT TCA TCA TCC AGT TTG				624
Gly Lys Phe Tyr Ser Ser Lys Ser Gly Gly Asn Ser Ser Ser Ser Leu	195	200	205	
GGT GAC ATA GTA CCT AGT TCC AGA AAA TCA ACA CCT CCA TCA TCT GCT				672
Gly Asp Ile Val Pro Ser Ser Arg Lys Ser Thr Pro Pro Ser Ser Ala	210	215	220	
ATA GAC ATA GAT GCT ACT GGC TTA GAT GCA GAA GAA AAT GAT ATT CCA				720
Ile Asp Ile Asp Ala Thr Gly Leu Asp Ala Glu Glu Asn Asp Ile Pro				

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225	230				235				240				
GCA AAC CAC CGC TCC CCT AAA CCC AGT GCA AAC AGT GTA ACG TCA CCC	Ala Asn His Arg Ser Pro Lys Pro Ser Ala Asn Ser Val Thr Ser Pro												768
	245				250							255	
CAC TCC AAA GAG AAA AGA ATG CCC TTC TTT AAG AAG ACA GAG CAC ACT	His Ser Lys Glu Lys Arg Met Pro Phe Phe Lys Lys Thr Glu His Thr												816
	260				265							270	
CCT CCG TAT GAT GTG GTA CCT TCC ATG CGA CCA GTG GTC CTA GTG GGC	Pro Pro Tyr Asp Val Val Pro Ser Met Arg Pro Val Val Leu Val Gly												864
	275				280							285	
CCT TCT CTG AAG GGC TAC GAG GTC ACA GAT ATG ATG CAA AAA GCG CTG	Pro Ser Leu Lys Gly Tyr Glu Val Thr Asp Met Met Gln Lys Ala Leu												912
	290				295							300	
TTT GAT TTT TTA AAA CAC AGA TTT GAA GGG CGG ATA TCC ATC ACA AGG	Phe Asp Phe Leu Lys His Arg Phe Glu Gly Arg Ile Ser Ile Thr Arg												960
	305				310							315	
GTC ACC GCT GAC ATC TCG CTT GCC AAA CGC TCG GTA TTA AAC AAT CCC	Val Thr Ala Asp Ile Ser Leu Ala Lys Arg Ser Val Leu Asn Asn Pro												1008
	325				330							335	
AGT AAG CAC GCA ATA ATA GAA AGA TCC AAC ACA AGG TCA AGC TTA GCG	Ser Lys His Ala Ile Ile Glu Arg Ser Asn Thr Arg Ser Ser Leu Ala												1056
	340				345							350	
GAA GTT CAG AGT GAA ATC GAA AGG ATT TTT GAA CTT GCA AGA ACA TTG	Glu Val Gln Ser Glu Ile Glu Arg Ile Phe Glu Leu Ala Arg Thr Leu												1104
	355				360							365	
CAG TTG GTG GTC CTT GAC GCG GAT ACA ATT AAT CAT CCA GCT CAA CTC	Gln Leu Val Val Leu Asp Ala Asp Thr Ile Asn His Pro Ala Gln Leu												1152
	370				375							380	
AGT AAA ACC TCC TTG GCC CCT ATT ATA GTA TAT GTA AAG ATT TCT TCT	Ser Lys Thr Ser Leu Ala Pro Ile Ile Val Tyr Val Lys Ile Ser Ser												1200
	385				390							395	
CCT AAG GTT TTA CAA AGG TTA ATA AAA TCT CGA GGG AAA TCT CAA GCT	Pro Lys Val Leu Gln Arg Leu Ile Lys Ser Arg Gly Lys Ser Gln Ala												1248
	405				410							415	
AAA CAC CTC AAC GTC CAG ATG GTA GCA GCT GAT AAA CTG GCT CAG TGT	Lys His Leu Asn Val Gln Met Val Ala Ala Asp Lys Leu Ala Gln Cys												1296
	420				425							430	
CCT CCA GAG CTG TTC GAT GTG ATC TTG GAT GAG AAC CAG CTT GAG GAT	Pro Pro Glu Leu Phe Asp Val Ile Leu Asp Glu Asn Gln Leu Glu Asp												1344
	435				440							445	
GCC TGT GAG CAC CTT GCC GAC TAT CTG GAG GCC TAC TGG AAG GCC ACC	Ala Cys Glu His Leu Ala Asp Tyr Leu Glu Ala Tyr Trp Lys Ala Thr												1392

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450	455	460	
CAT CCT CCC AGC AGT AGC CTC CCC AAC CCT CTC CTT AGC CGT ACA TTA			1440
His Pro Pro Ser Ser Ser Leu Pro Asn Pro Leu Leu Ser Arg Thr Leu			
465	470	475	480
GCC ACT TCA AGT CTG CCT CTT AGC CCC ACC CTA GCC TCT AAT TCA CAG			1488
Ala Thr Ser Ser Leu Pro Leu Ser Pro Thr Leu Ala Ser Asn Ser Gln			
	485	490	495
GGT TCT CAA GGT GAT CAG AGG ACT GAT CGC TCC GCT CCT ATC CGT TCT			1536
Gly Ser Gln Gly Asp Gln Arg Thr Asp Arg Ser Ala Pro Ile Arg Ser			
	500	505	510
GCT TCC CAA GCT GAA GAA GAA CCT AGT GTG GAA CCA GTC AAG AAA TCC			1584
Ala Ser Gln Ala Glu Glu Glu Pro Ser Val Glu Pro Val Lys Lys Ser			
	515	520	525
CAG CAC CGC TCT TCC TCC TCA GCC CCA CAC CAC AAC CAT CGC AGT GGG			1632
Gln His Arg Ser Ser Ser Ser Ala Pro His His Asn His Arg Ser Gly			
	530	535	540
ACA AGT CGC GGC CTC TCC AGG CAA GAG ACA TTT GAC TCG GAA ACC CAG			1680
Thr Ser Arg Gly Leu Ser Arg Gln Glu Thr Phe Asp Ser Glu Thr Gln			
	545	550	555
GAG AGT CGA GAC TCT GCC TAC GTA GAG CCA AAG GAA GAT TAT TCC CAT			1728
Glu Ser Arg Asp Ser Ala Tyr Val Glu Pro Lys Glu Asp Tyr Ser His			
	565	570	575
GAC CAC GTG GAC CAC TAT GCC TCA CAC CGT GAC CAC AAC CAC AGA GAC			1776
Asp His Val Asp His Tyr Ala Ser His Arg Asp His Asn His Arg Asp			
	580	585	590
GAG ACC CAC GGG AGC AGT GAC CAC AGA CAC AGG GAG TCC CGG CAC CGT			1824
Glu Thr His Gly Ser Ser Asp His Arg His Arg Glu Ser Arg His Arg			
	595	600	605
TCC CGG GAC GTG GAT CGA GAG CAG GAC CAC AAC GAG TGC AAC AAG CAG			1872
Ser Arg Asp Val Asp Arg Glu Gln Asp His Asn Glu Cys Asn Lys Gln			
	610	615	620
CGC AGC CGT CAT AAA TCC AAG GAT CGC TAC TGT GAA AAG GAT GGA GAA			1920
Arg Ser Arg His Lys Ser Lys Asp Arg Tyr Cys Glu Lys Asp Gly Glu			
	625	630	640
GTG ATA TCA AAA AAA CGG AAT GAG GCT GGG GAG TGG AAC AGG GAT GTT			1968
Val Ile Ser Lys Lys Arg Asn Glu Ala Gly Glu Trp Asn Arg Asp Val			
	645	650	655
TAC ATC CCC CAA TGAGTTTTGC CCTTTTGTGT TTTTTTTTTT TTTTTTTTGA			2020
Tyr Ile Pro Gln			
	660		
AGTCTTGTAT AACTAACAGC ATCCCCAAAA CAAAAAGTCT TTGGGGTCTA CACTGCAATC			2080

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ATATGTGATC TGTCTTGTA TATTTTGTAT TATTGCTGTT GCTTGAATAG CAATAGCATG	2140
GATAGAGTAT TGAGATACTT TTTCTTTTGT AAGTGCTACA TAAATTGGCC TGGTATGGCT	2200
GCAGTCCTCC GGTTCATAC TGGACTCTTC AAAAAGTGT TTGGGTAGCT GCCACTTGAA	2260
CAAAATCTGT TGCCACCCAG GTGATGTTAG TGTTTTAAGA AATGTAGTTG ATGTATCCAA	2320
CAAGCCAGAA TCAGCACAGA TAAAAAGTGG AATTCTTGT TTCTCCAGAT TTTTAATACG	2380
TTAATACGCA GGCATCTGAT TTGCATATTC ATTCATGGAC CACTGTTTCT TGCTTGTACC	2440
TCTGGCTGAC TAAATTTGGG GACAGATTCA GTCTTGCTT ACACAAAGGG GATCATAAAG	2500
TTAGAATCTA TTTTCTATGT ACTAGTACTG TGTACTGTAT AGACAGTTTG TAAATGTTAT	2560
TTCTGCAAAC AACACCTCC TTATTATATA TAATATATAT ATATATATCA GTTTGATCAC	2620
ACTATTTTAG AGTC	2634

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1823 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 69..1631
- (D) OTHER INFORMATION: /standard_name= "Beta-4"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

AGCCCAGCCT CGGGGGCCAG CCCCTCCGC CCACCGCACA CGGGCTGGCC ATGCGGCGGC	60
TCTGAACG ATG TCC TCC TCC TCC TAC GCC AAG AAC GGG ACC GCG GAC GGG	110
Met Ser Ser Ser Ser Tyr Ala Lys Asn Gly Thr Ala Asp Gly	
1 5 10	
CCG CAC TCC CCC ACC TCG CAG GTG GCC CGA GGC ACC ACA ACC CGG AGG	158
Pro His Ser Pro Thr Ser Gln Val Ala Arg Gly Thr Thr Thr Arg Arg	
15 20 25 30	
AGC AGG TTG AAA AGA TCC GAT GGC AGC ACC ACT TCG ACC AGC TTC ATC	206
Ser Arg Leu Lys Arg Ser Asp Gly Ser Thr Thr Ser Thr Ser Phe Ile	
35 40 45	
CTC AGA CAG GGT TCA GCG GAT TCC TAC ACA AGC AGG CCG TCT GAC TCC	254
Leu Arg Gln Gly Ser Ala Asp Ser Tyr Thr Ser Arg Pro Ser Asp Ser	
50 55 60	

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GAT	GTC	TCT	TTG	GAA	GAG	GAC	CGG	GAA	GCA	ATT	CGA	CAG	GAG	AGA	GAA	302
Asp	Val	Ser	Leu	Glu	Glu	Asp	Arg	Glu	Ala	Ile	Arg	Gln	Glu	Arg	Glu	
		65					70					75				
CAG	CAA	GCA	GCT	ATC	CAG	CTT	GAG	AGA	GCA	AAG	TCC	AAA	CCT	GTA	GCA	350
Gln	Gln	Ala	Ala	Ile	Gln	Leu	Glu	Arg	Ala	Lys	Ser	Lys	Pro	Val	Ala	
	80					85					90					
TTT	GCC	GTG	AAG	ACA	AAT	GTG	AGC	TAC	TGC	GGC	GCC	CTG	GAC	GAG	GAT	398
Phe	Ala	Val	Lys	Thr	Asn	Val	Ser	Tyr	Cys	Gly	Ala	Leu	Asp	Glu	Asp	
	95				100					105					110	
GTG	CCT	GTT	CCA	AGC	ACA	GCT	ATC	TCC	TTT	GAT	GCT	AAA	GAC	TTT	CTA	446
Val	Pro	Val	Pro	Ser	Thr	Ala	Ile	Ser	Phe	Asp	Ala	Lys	Asp	Phe	Leu	
				115					120					125		
CAT	ATT	AAA	GAG	AAA	TAT	AAC	AAT	GAT	TGG	TGG	ATA	GGA	AGG	CTG	GTG	494
His	Ile	Lys	Glu	Lys	Tyr	Asn	Asn	Asp	Trp	Trp	Ile	Gly	Arg	Leu	Val	
			130					135					140			
AAA	GAG	GGC	TGT	GAA	ATT	GGC	TTC	ATT	CCA	AGT	CCA	CTC	AGA	TTG	GAG	542
Lys	Glu	Gly	Cys	Glu	Ile	Gly	Phe	Ile	Pro	Ser	Pro	Leu	Arg	Leu	Glu	
		145				150						155				
AAC	ATA	CGG	ATC	CAG	CAA	GAA	CAA	AAA	AGA	GGA	CGT	TTT	CAC	GGA	GGG	590
Asn	Ile	Arg	Ile	Gln	Gln	Glu	Gln	Lys	Arg	Gly	Arg	Phe	His	Gly	Gly	
	160					165					170					
AAA	TCA	AGT	GGA	AAT	TCT	TCT	TCA	AGT	CTT	GGA	GAA	ATG	GTA	TCT	GGG	638
Lys	Ser	Ser	Gly	Asn	Ser	Ser	Ser	Ser	Leu	Gly	Glu	Met	Val	Ser	Gly	
	175				180					185					190	
ACA	TTC	CGA	GCA	ACT	CCC	ACA	TCA	ACA	GCA	AAA	CAG	AAG	CAA	AAA	GTG	686
Thr	Phe	Arg	Ala	Thr	Pro	Thr	Ser	Thr	Ala	Lys	Gln	Lys	Gln	Lys	Val	
				195					200					205		
ACG	GAG	CAC	ATT	CCT	CCT	TAC	GAT	GTT	GTA	CCG	TCA	ATG	CGT	CCG	GTG	734
Thr	Glu	His	Ile	Pro	Pro	Tyr	Asp	Val	Val	Pro	Ser	Met	Arg	Pro	Val	
			210					215					220			
GTG	TTA	GTG	GGG	CCG	TCA	CTG	AAA	GGT	TAC	GAG	GTA	ACA	GAC	ATG	ATG	782
Val	Leu	Val	Gly	Pro	Ser	Leu	Lys	Gly	Tyr	Glu	Val	Thr	Asp	Met	Met	
		225					230					235				
CAG	AAA	GCC	CTC	TTT	GAT	TCC	CTG	AAG	CAC	AGG	TTT	GAT	GGG	AGG	ATT	830
Gln	Lys	Ala	Leu	Phe	Asp	Ser	Leu	Lys	His	Arg	Phe	Asp	Gly	Arg	Ile	
	240					245					250					
TCA	ATA	ACG	AGA	GTG	ACA	GCT	GAC	ATT	TCT	CTT	GCT	AAG	AGG	TCT	GTC	878
Ser	Ile	Thr	Arg	Val	Thr	Ala	Asp	Ile	Ser	Leu	Ala	Lys	Arg	Ser	Val	
	255				260					265					270	
CTA	AAT	AAT	CCC	AGC	AAG	AGA	GCA	ATA	ATT	GAA	CGT	TCG	AAC	ACC	CGG	926
Leu	Asn	Asn	Pro	Ser	Lys	Arg	Ala	Ile	Ile	Glu	Arg	Ser	Asn	Thr	Arg	
				275					280					285		

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TCC	AGC	TTA	GCG	GAA	GTA	CAA	AGT	GAA	ATT	GAA	AGA	ATC	TTT	GAG	TTG	974
Ser	Ser	Leu	Ala	Glu	Val	Gln	Ser	Glu	Ile	Glu	Arg	Ile	Phe	Glu	Leu	
			290					295					300			
GCA	AGA	TCT	TTG	CAA	CTG	GTT	GTT	CTT	GAT	GCA	GAC	ACC	ATC	AAT	CAC	1022
Ala	Arg	Ser	Leu	Gln	Leu	Val	Val	Leu	Asp	Ala	Asp	Thr	Ile	Asn	His	
		305					310					315				
CCA	GCA	CAA	CTT	ATA	AAG	ACT	TCC	TTA	GCA	CCA	ATT	ATT	GTT	CAT	GTA	1070
Pro	Ala	Gln	Leu	Ile	Lys	Thr	Ser	Leu	Ala	Pro	Ile	Ile	Val	His	Val	
	320					325					330					
AAA	GTC	TCA	TCT	CCA	AAG	GTT	TTA	CAG	CGG	TTG	ATT	AAA	TCT	AGA	GGA	1118
Lys	Val	Ser	Ser	Pro	Lys	Val	Leu	Gln	Arg	Leu	Ile	Lys	Ser	Arg	Gly	
	335				340					345					350	
AAG	TCA	CAA	AGT	AAA	CAC	TTG	AAT	GTT	CAA	CTG	GTG	GCA	GCT	GAT	AAA	1166
Lys	Ser	Gln	Ser	Lys	His	Leu	Asn	Val	Gln	Leu	Val	Ala	Ala	Asp	Lys	
				355					360					365		
CTT	GCA	CAA	TGC	CCC	CCA	GAA	ATG	TTT	GAT	GTT	ATA	TTG	GAT	GAA	AAT	1214
Leu	Ala	Gln	Cys	Pro	Pro	Glu	Met	Phe	Asp	Val	Ile	Leu	Asp	Glu	Asn	
			370					375					380			
CAG	CTT	GAG	GAT	GCA	TGT	GAA	CAT	CTA	GGG	GAG	TAC	CTG	GAG	GCG	TAC	1262
Gln	Leu	Glu	Asp	Ala	Cys	Glu	His	Leu	Gly	Glu	Tyr	Leu	Glu	Ala	Tyr	
		385					390					395				
TGG	CGT	GCC	ACC	CAC	ACA	ACC	AGT	AGC	ACA	CCC	ATG	ACC	CCG	CTG	CTG	1310
Trp	Arg	Ala	Thr	His	Thr	Thr	Ser	Ser	Thr	Pro	Met	Thr	Pro	Leu	Leu	
	400					405					410					
GGA	AGG	AAT	TTG	GGC	TCC	ACG	GCA	CTC	TCA	CCA	TAT	CCC	ACA	GCA	ATT	1358
Gly	Arg	Asn	Leu	Gly	Ser	Thr	Ala	Leu	Ser	Pro	Tyr	Pro	Thr	Ala	Ile	
	415				420					425					430	
TCT	GGG	TTA	CAG	AGT	CAG	CGA	ATG	AGG	CAC	AGC	AAC	CAC	TCC	ACA	GAG	1406
Ser	Gly	Leu	Gln	Ser	Gln	Arg	Met	Arg	His	Ser	Asn	His	Ser	Thr	Glu	
				435					440					445		
AAC	TCT	CCA	ATT	GAA	AGA	CGA	AGT	CTA	ATG	ACC	TCT	GAT	GAA	AAT	TAT	1454
Asn	Ser	Pro	Ile	Glu	Arg	Arg	Ser	Leu	Met	Thr	Ser	Asp	Glu	Asn	Tyr	
		450						455					460			
CAC	AAT	GAA	AGG	GCT	CGG	AAG	AGT	AGG	AAC	CGC	TTG	TCT	TCC	AGT	TCT	1502
His	Asn	Glu	Arg	Ala	Arg	Lys	Ser	Arg	Asn	Arg	Leu	Ser	Ser	Ser	Ser	
		465					470					475				
CAG	CAT	AGC	CGA	GAT	CAT	TAC	CCT	CTT	GTG	GAA	GAA	GAT	TAC	CCT	GAC	1550
Gln	His	Ser	Arg	Asp	His	Tyr	Pro	Leu	Val	Glu	Glu	Asp	Tyr	Pro	Asp	
		480				485					490					
TCA	TAC	CAG	GAC	ACT	TAC	AAA	CCC	CAT	AGG	AAC	CGA	GGA	TCA	CCT	GGG	1598
Ser	Tyr	Gln	Asp	Thr	Tyr	Lys	Pro	His	Arg	Asn	Arg	Gly	Ser	Pro	Gly	
	495				500					505					510	

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GGA TAT AGC CAT GAC TCC CGA CAT AGG CTT TGAGTCTAAT GAAACAAAAA 1648
 Gly Tyr Ser His Asp Ser Arg His Arg Leu
 515 520

ATATTCATCT GTTGACAATT TGCCATAGCA GTGCTAGGAT AAACCAATCA TCTTAACTTG 1708

GCTAACATAG CACAGTATTT ACTGTGCTAA TGGGCTGCTG TCATTTTATG CTAAGTAAGG 1768

GGCAAAAAAA AAAATTACAT TATGCCCTTG AGTCTAGATG GATATTAGAT GCCCCG 1823

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 520 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met Ser Ser Ser Ser Tyr Ala Lys Asn Gly Thr Ala Asp Gly Pro His
 1 5 10 15
 Ser Pro Thr Ser Gln Val Ala Arg Gly Thr Thr Thr Arg Arg Ser Arg
 20 25 30
 Leu Lys Arg Ser Asp Gly Ser Thr Thr Ser Thr Ser Phe Ile Leu Arg
 35 40 45
 Gln Gly Ser Ala Asp Ser Tyr Thr Ser Arg Pro Ser Asp Ser Asp Val
 50 55 60
 Ser Leu Glu Glu Asp Arg Glu Ala Ile Arg Gln Glu Arg Glu Gln Gln
 65 70 75 80
 Ala Ala Ile Gln Leu Glu Arg Ala Lys Ser Lys Pro Val Ala Phe Ala
 85 90 95
 Val Lys Thr Asn Val Ser Tyr Cys Gly Ala Leu Asp Glu Asp Val Pro
 100 105 110
 Val Pro Ser Thr Ala Ile Ser Phe Asp Ala Lys Asp Phe Leu His Ile
 115 120 125
 Lys Glu Lys Tyr Asn Asn Asp Trp Trp Ile Gly Arg Leu Val Lys Glu
 130 135 140
 Gly Cys Glu Ile Gly Phe Ile Pro Ser Pro Leu Arg Leu Glu Asn Ile
 145 150 155 160
 Arg Ile Gln Gln Glu Gln Lys Arg Gly Arg Phe His Gly Gly Lys Ser
 165 170 175
 Ser Gly Asn Ser Ser Ser Ser Leu Gly Glu Met Val Ser Gly Thr Phe
 180 185 190

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Arg Ala Thr Pro Thr Ser Thr Ala Lys Gln Lys Gln Lys Val Thr Glu
 195 200 205
 His Ile Pro Pro Tyr Asp Val Val Pro Ser Met Arg Pro Val Val Leu
 210 215 220
 Val Gly Pro Ser Leu Lys Gly Tyr Glu Val Thr Asp Met Met Gln Lys
 225 230 235 240
 Ala Leu Phe Asp Ser Leu Lys His Arg Phe Asp Gly Arg Ile Ser Ile
 245 250 255
 Thr Arg Val Thr Ala Asp Ile Ser Leu Ala Lys Arg Ser Val Leu Asn
 260 265 270
 Asn Pro Ser Lys Arg Ala Ile Ile Glu Arg Ser Asn Thr Arg Ser Ser
 275 280 285
 Leu Ala Glu Val Gln Ser Glu Ile Glu Arg Ile Phe Glu Leu Ala Arg
 290 295 300
 Ser Leu Gln Leu Val Val Leu Asp Ala Asp Thr Ile Asn His Pro Ala
 305 310 315 320
 Gln Leu Ile Lys Thr Ser Leu Ala Pro Ile Ile Val His Val Lys Val
 325 330 335
 Ser Ser Pro Lys Val Leu Gln Arg Leu Ile Lys Ser Arg Gly Lys Ser
 340 345 350
 Gln Ser Lys His Leu Asn Val Gln Leu Val Ala Ala Asp Lys Leu Ala
 355 360 365
 Gln Cys Pro Pro Glu Met Phe Asp Val Ile Leu Asp Glu Asn Gln Leu
 370 375 380
 Glu Asp Ala Cys Glu His Leu Gly Glu Tyr Leu Glu Ala Tyr Trp Arg
 385 390 395 400
 Ala Thr His Thr Thr Ser Ser Thr Pro Met Thr Pro Leu Leu Gly Arg
 405 410 415
 Asn Leu Gly Ser Thr Ala Leu Ser Pro Tyr Pro Thr Ala Ile Ser Gly
 420 425 430
 Leu Gln Ser Gln Arg Met Arg His Ser Asn His Ser Thr Glu Asn Ser
 435 440 445
 Pro Ile Glu Arg Arg Ser Leu Met Thr Ser Asp Glu Asn Tyr His Asn
 450 455 460
 Glu Arg Ala Arg Lys Ser Arg Asn Arg Leu Ser Ser Ser Ser Gln His
 465 470 475 480
 Ser Arg Asp His Tyr Pro Leu Val Glu Glu Asp Tyr Pro Asp Ser Tyr
 485 490 495

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Gln Asp Thr Tyr Lys Pro His Arg Asn Arg Gly Ser Pro Gly Gly Tyr
 500 505 510

Ser His Asp Ser Arg His Arg Leu
 515 520

(2) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 3636 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 35..3346
 (D) OTHER INFORMATION: /standard_name= "Alpha-2a"

- (ix) FEATURE:
 (A) NAME/KEY: 5'UTR
 (B) LOCATION: 1..34

- (ix) FEATURE:
 (A) NAME/KEY: 3'UTR
 (B) LOCATION: 3347..3636

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GCGGGGGAGG GGGCATTGAT CTTGATCGC GAAG ATG GCT GCT GGC TGC CTG	52
Met Ala Ala Gly Cys Leu	
1 5	
CTG GCC TTG ACT CTG ACA CTT TTC CAA TCT TTG CTC ATC GGC CCC TCG	100
Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser Leu Leu Ile Gly Pro Ser	
10 15 20	
TCG GAG GAG CCG TTC CCT TCG GCC GTC ACT ATC AAA TCA TGG GTG GAT	148
Ser Glu Glu Pro Phe Pro Ser Ala Val Thr Ile Lys Ser Trp Val Asp	
25 30 35	
AAG ATG CAA GAA GAC CTT GTC ACA CTG GCA AAA ACA GCA AGT GGA GTC	196
Lys Met Gln Glu Asp Leu Val Thr Leu Ala Lys Thr Ala Ser Gly Val	
40 45 50	
AAT CAG CTT GTT GAT ATT TAT GAG AAA TAT CAA GAT TTG TAT ACT GTG	244
Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr Gln Asp Leu Tyr Thr Val	
55 60 65 70	
GAA CCA AAT AAT GCA CGC CAG CTG GTA GAA ATT GCA GCC AGG GAT ATT	292
Glu Pro Asn Asn Ala Arg Gln Leu Val Glu Ile Ala Ala Arg Asp Ile	
75 80 85	

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GAG	AAA	CTT	CTG	AGC	AAC	AGA	TCT	AAA	GCC	CTG	GTG	AGC	CTG	GCA	TTG	340
Glu	Lys	Leu	Leu	Ser	Asn	Arg	Ser	Lys	Ala	Leu	Val	Ser	Leu	Ala	Leu	
			90					95					100			
GAA	GCG	GAG	AAA	GTT	CAA	GCA	GCT	CAC	CAG	TGG	AGA	GAA	GAT	TTT	GCA	388
Glu	Ala	Glu	Lys	Val	Gln	Ala	Ala	His	Gln	Trp	Arg	Glu	Asp	Phe	Ala	
		105					110					115				
AGC	AAT	GAA	GTT	GTC	TAC	TAC	AAT	GCA	AAG	GAT	GAT	CTC	GAT	CCT	GAG	436
Ser	Asn	Glu	Val	Val	Tyr		Asn	Ala	Lys	Asp		Leu	Asp	Pro	Glu	
	120				125					130						
AAA	AAT	GAC	AGT	GAG	CCA	GGC	AGC	CAG	AGG	ATA	AAA	CCT	GTT	TTC	ATT	484
Lys	Asn	Asp	Ser	Glu	Pro	Gly	Ser	Gln	Arg	Ile	Lys	Pro	Val	Phe	Ile	
135					140				145						150	
GAA	GAT	GCT	AAT	TTT	GGA	CGA	CAA	ATA	TCT	TAT	CAG	CAC	GCA	GCA	GTC	532
Glu	Asp	Ala	Asn	Phe	Gly	Arg	Gln	Ile	Ser	Tyr	Gln	His	Ala	Ala	Val	
				155					160					165		
CAT	ATT	CCT	ACT	GAC	ATC	TAT	GAG	GGC	TCA	ACA	ATT	GTG	TTA	AAT	GAA	580
His	Ile	Pro	Thr	Asp	Ile	Tyr	Glu	Gly	Ser	Thr	Ile	Val	Leu	Asn	Glu	
			170					175					180			
CTC	AAC	TGG	ACA	AGT	GCC	TTA	GAT	GAA	GTT	TTC	AAA	AAG	AAT	CGC	GAG	628
Leu	Asn	Trp	Thr	Ser	Ala	Leu	Asp	Glu	Val	Phe	Lys	Lys	Asn	Arg	Glu	
		185					190					195				
GAA	GAC	CCT	TCA	TTA	TTG	TGG	CAG	GTT	TTT	GGC	AGT	GCC	ACT	GGC	CTA	676
Glu	Asp	Pro	Ser	Leu	Leu	Trp	Gln	Val	Phe	Gly	Ser	Ala	Thr	Gly	Leu	
	200					205				210						
GCT	CGA	TAT	TAT	CCA	GCT	TCA	CCA	TGG	GTT	GAT	AAT	AGT	AGA	ACT	CCA	724
Ala	Arg	Tyr	Tyr	Pro	Ala	Ser	Pro	Trp	Val	Asp	Asn	Ser	Arg	Thr	Pro	
215					220					225					230	
AAT	AAG	ATT	GAC	CTT	TAT	GAT	GTA	CGC	AGA	AGA	CCA	TGG	TAC	ATC	CAA	772
Asn	Lys	Ile	Asp	Leu	Tyr	Asp	Val	Arg	Arg	Arg	Pro	Trp	Tyr	Ile	Gln	
			235					240						245		
GGA	GCT	GCA	TCT	CCT	AAA	GAC	ATG	CTT	ATT	CTG	GTG	GAT	GTG	AGT	GGA	820
Gly	Ala	Ala	Ser	Pro	Lys	Asp	Met	Leu	Ile	Leu	Val	Asp	Val	Ser	Gly	
			250				255						260			
AGT	GTT	AGT	GGA	TTG	ACA	CTT	AAA	CTG	ATC	CGA	ACA	TCT	GTC	TCC	GAA	868
Ser	Val	Ser	Gly	Leu	Thr	Leu	Lys	Leu	Ile	Arg	Thr	Ser	Val	Ser	Glu	
		265					270					275				
ATG	TTA	GAA	ACC	CTC	TCA	GAT	GAT	GAT	TTC	GTG	AAT	GTA	GCT	TCA	TTT	916
Met	Leu	Glu	Thr	Leu	Ser	Asp	Asp	Asp	Phe	Val	Asn	Val	Ala	Ser	Phe	
	280					285					290					
AAC	AGC	AAT	GCT	CAG	GAT	GTA	AGC	TGT	TTT	CAG	CAC	CTT	GTC	CAA	GCA	964
Asn	Ser	Asn	Ala	Gln	Asp	Val	Ser	Cys	Phe	Gln	His	Leu	Val	Gln	Ala	
295					300					305					310	

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AAT	GTA	AGA	AAT	AAA	AAA	GTG	TTG	AAA	GAC	GCG	GTG	AAT	AAT	ATC	ACA	1012
Asn	Val	Arg	Asn	Lys	Lys	Val	Leu	Lys	Asp	Ala	Val	Asn	Asn	Ile	Thr	
				315					320					325		
GCC	AAA	GGA	ATT	ACA	GAT	TAT	AAG	AAG	GGC	TTT	AGT	TTT	GCT	TTT	GAA	1060
Ala	Lys	Gly	Ile	Thr	Asp	Tyr	Lys	Lys	Gly	Phe	Ser	Phe	Ala	Phe	Glu	
			330					335					340			
CAG	CTG	CTT	AAT	TAT	AAT	GTT	TCC	AGA	GCA	AAC	TGC	AAT	AAG	ATT	ATT	1108
Gln	Leu	Leu	Asn	Tyr	Asn	Val	Ser	Arg	Ala	Asn	Cys	Asn	Lys	Ile	Ile	
		345					350					355				
ATG	CTA	TTC	ACG	GAT	GGA	GGA	GAA	GAG	AGA	GCC	CAG	GAG	ATA	TTT	AAC	1156
Met	Leu	Phe	Thr	Asp	Gly	Gly	Glu	Glu	Arg	Ala	Gln	Glu	Ile	Phe	Asn	
	360					365					370					
AAA	TAC	AAT	AAA	GAT	AAA	AAA	GTA	CGT	GTA	TTC	AGG	TTT	TCA	GTT	GGT	1204
Lys	Tyr	Asn	Lys	Asp	Lys	Lys	Val	Arg	Val	Phe	Arg	Phe	Ser	Val	Gly	
375					380					385					390	
CAA	CAC	AAT	TAT	GAG	AGA	GGA	CCT	ATT	CAG	TGG	ATG	GCC	TGT	GAA	AAC	1252
Gln	His	Asn	Tyr	Glu	Arg	Gly	Pro	Ile	Gln	Trp	Met	Ala	Cys	Glu	Asn	
				395					400					405		
AAA	GGT	TAT	TAT	TAT	GAA	ATT	CCT	TCC	ATT	GGT	GCA	ATA	AGA	ATC	AAT	1300
Lys	Gly	Tyr	Tyr	Tyr	Glu	Ile	Pro	Ser	Ile	Gly	Ala	Ile	Arg	Ile	Asn	
			410				415						420			
ACT	CAG	GAA	TAT	TTG	GAT	GTT	TTG	GGA	AGA	CCA	ATG	GTT	TTA	GCA	GGA	1348
Thr	Gln	Glu	Tyr	Leu	Asp	Val	Leu	Gly	Arg	Pro	Met	Val	Leu	Ala	Gly	
		425					430					435				
GAC	AAA	GCT	AAG	CAA	GTC	CAA	TGG	ACA	AAT	GTG	TAC	CTG	GAT	GCA	TTG	1396
Asp	Lys	Ala	Lys	Gln	Val	Gln	Trp	Thr	Asn	Val	Tyr	Leu	Asp	Ala	Leu	
	440					445					450					
GAA	CTG	GGA	CTT	GTC	ATT	ACT	GGA	ACT	CTT	CCG	GTC	TTC	AAC	ATA	ACC	1444
Glu	Leu	Gly	Leu	Val	Ile	Thr	Gly	Thr	Leu	Pro	Val	Phe	Asn	Ile	Thr	
455					460					465					470	
GGC	CAA	TTT	GAA	AAT	AAG	ACA	AAC	TTA	AAG	AAC	CAG	CTG	ATT	CTT	GGT	1492
Gly	Gln	Phe	Glu	Asn	Lys	Thr	Asn	Leu	Lys	Asn	Gln	Leu	Ile	Leu	Gly	
				475				480						485		
GTG	ATG	GGA	GTA	GAT	GTG	TCT	TTG	GAA	GAT	ATT	AAA	AGA	CTG	ACA	CCA	1540
Val	Met	Gly	Val	Asp	Val	Ser	Leu	Glu	Asp	Ile	Lys	Arg	Leu	Thr	Pro	
			490				495						500			
CGT	TTT	ACA	CTG	TGC	CCC	AAT	GGG	TAT	TAC	TTT	GCA	ATC	GAT	CCT	AAT	1588
Arg	Phe	Thr	Leu	Cys	Pro	Asn	Gly	Tyr	Tyr	Phe	Ala	Ile	Asp	Pro	Asn	
		505					510					515				
GGT	TAT	GTT	TTA	TTA	CAT	CCA	AAT	CTT	CAG	CCA	AAG	CCT	ATT	GGT	GTA	1636
Gly	Tyr	Val	Leu	Leu	His	Pro	Asn	Leu	Gln	Pro	Lys	Pro	Ile	Gly	Val	
	520					525					530					

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GGT Gly 535	ATA Ile	CCA Pro	ACA Thr	ATT Ile	AAT Asn 540	TTA Leu	AGA Arg	AAA Lys	AGG Arg 545	AGA Arg	CCC Pro	AAT Asn	ATC Ile	CAG Gln	AAC Asn 550	1684
CCC Pro	AAA Lys	TCT Ser	CAG Gln 555	GAG Glu 555	CCA Pro	GTA Val	ACA Thr	TTG Leu 560	GAT Asp 560	TTC Phe	CTT Leu	GAT Asp	GCA Ala	GAG Glu 565	TTA Leu	1732
GAG Glu	AAT Asn	GAT Asp	ATT Ile 570	AAA Lys	GTG Val	GAG Glu	ATT Ile	CGA Arg 575	AAT Asn	AAG Lys	ATG Met	ATT Ile	GAT Asp 580	GGG Gly	GAA Glu	1780
AGT Ser	GGA Gly	GAA Glu 585	AAA Lys	ACA Thr	TTC Phe	AGA Arg 590	ACT Thr	CTG Leu	GTT Val	AAA Lys	TCT Ser	CAA Gln 595	GAT Asp	GAG Glu	AGA Arg	1828
TAT Tyr 600	ATT Ile	GAC Asp	AAA Lys	GGA Gly	AAC Asn 605	AGG Arg	ACA Thr	TAC Tyr	ACA Thr	TGG Trp	ACA Thr	CCT Pro	GTC Val	AAT Asn	GGC Gly	1876
ACA Thr 615	GAT Asp	TAC Tyr	AGT Ser	TTG Leu	GCC Ala 620	TTG Leu	GTA Val	TTA Leu	CCA Pro	ACC Thr 625	TAC Tyr	AGT Ser	TTT Phe	TAC Tyr	TAT Tyr 630	1924
ATA Ile	AAA Lys	GCC Ala	AAA Lys	CTA Leu 635	GAA Glu	GAG Glu	ACA Thr	ATA Ile	ACT Thr 640	CAG Gln	GCC Ala	AGA Arg	TAT Tyr	TCG Ser	GAA Glu 645	1972
ACC Thr	CTG Leu	AAG Lys	CCA Pro 650	GAT Asp	AAT Asn	TTT Phe	GAA Glu	GAA Glu 655	TCT Ser	GGC Gly	TAT Tyr	ACA Thr	TTC Phe 660	ATA Ile	GCA Ala	2020
CCA Pro	AGA Arg	GAT Asp 665	TAC Tyr	TGC Cys	AAT Asn	GAC Asp	CTG Leu 670	AAA Lys	ATA Ile	TCG Ser	GAT Asp	AAT Asn	AAC Asn	ACT Thr	GAA Glu	2068
TTT Phe 680	CTT Leu	TTA Leu	AAT Asn	TTC Phe	AAC Asn 685	GAG Glu 685	TTT Phe	ATT Ile	GAT Asp	AGA Arg	AAA Lys 690	ACT Thr	CCA Pro	AAC Asn	AAC Asn	2116
CCA Pro 695	TCA Ser	TGT Cys	AAC Asn	GCG Ala	GAT Asp 700	TTG Leu	ATT Ile	AAT Asn	AGA Arg	GTC Val 705	TTG Leu	CTT Leu	GAT Asp	GCA Ala	GGC Gly 710	2164
TTT Phe	ACA Thr	AAT Asn	GAA Glu	CTT Leu 715	GTC Val	CAA Gln	AAT Asn	TAC Tyr	TGG Trp 720	AGT Ser	AAG Lys	CAG Gln	AAA Lys	AAT Asn 725	ATC Ile	2212
AAG Lys	GGA Gly	GTG Val	AAA Lys 730	GCA Ala	CGA Arg	TTT Phe	GTT Val	GTG Val 735	ACT Thr	GAT Asp	GGT Gly	GGG Gly	ATT Ile 740	ACC Thr	AGA Arg	2260
GTT Val	TAT Tyr	CCC Pro 745	AAA Lys	GAG Glu	GCT Ala	GGA Gly	GAA Glu	AAT Asn 750	TGG Trp	CAA Gln	GAA Glu	AAC Asn 755	CCA Pro	GAG Glu	ACA Thr	2308

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TAT Tyr	GAG Glu	GAC Asp	AGC Ser	TTC Phe	TAT Tyr	AAA Lys	AGG Arg	AGC Ser	CTA Leu	GAT Asp	AAT Asn	GAT Asp	AAC Asn	TAT Tyr	GTT Val	2356
760						765				770						
TTC Phe	ACT Thr	GCT Ala	CCC Pro	TAC Tyr	TTT Phe	AAC Asn	AAA Lys	AGT Ser	GGA Gly	CCT Pro	GGT Gly	GCC Ala	TAT Tyr	GAA Glu	TCG Ser	2404
775					780					785					790	
GGC Gly	ATT Ile	ATG Met	GTA Val	AGC Ser	AAA Lys	GCT Ala	GTA Val	GAA Glu	ATA Ile	TAT Tyr	ATT Ile	CAA Gln	GGG Gly	AAA Lys	CTT Leu	2452
				795					800					805		
CTT Leu	AAA Lys	CCT Pro	GCA Ala	GTT Val	GTT Val	GGA Gly	ATT Ile	AAA Lys	ATT Ile	GAT Asp	GTA Val	AAT Asn	TCC Ser	TGG Trp	ATA Ile	2500
			810					815					820			
GAG Glu	AAT Asn	TTC Phe	ACC Thr	AAA Lys	ACC Thr	TCA Ser	ATC Ile	AGA Arg	GAT Asp	CCG Pro	TGT Cys	GCT Ala	GGT Gly	CCA Pro	GTT Val	2548
		825					830					835				
TGT Cys	GAC Asp	TGC Cys	AAA Lys	AGA Arg	AAC Asn	AGT Ser	GAC Asp	GTA Val	ATG Met	GAT Asp	TGT Cys	GTG Val	ATT Ile	CTG Leu	GAT Asp	2596
	840					845					850					
GAT Asp	GGT Gly	GGG Gly	TTT Phe	CTT Leu	CTG Leu	ATG Met	GCA Ala	AAT Asn	CAT His	GAT Asp	GAT Asp	TAT Tyr	ACT Thr	AAT Asn	CAG Gln	2644
855					860					865					870	
ATT Ile	GGA Gly	AGA Arg	TTT Phe	TTT Phe	GGA Gly	GAG Glu	ATT Ile	GAT Asp	CCC Pro	AGC Ser	TTG Leu	ATG Met	AGA Arg	CAC His	CTG Leu	2692
				875					880					885		
GTT Val	AAT Asn	ATA Ile	TCA Ser	GTT Val	TAT Tyr	GCT Ala	TTT Phe	AAC Asn	AAA Lys	TCT Ser	TAT Tyr	GAT Asp	TAT Tyr	CAG Gln	TCA Ser	2740
			890					895					900			
GTA Val	TGT Cys	GAG Glu	CCC Pro	GGT Gly	GCT Ala	GCA Ala	CCA Pro	AAA Lys	CAA Gln	GGA Gly	GCA Ala	GGA Gly	CAT His	CGC Arg	TCA Ser	2788
		905					910					915				
GCA Ala	TAT Tyr	GTG Val	CCA Pro	TCA Ser	GTA Val	GCA Ala	GAC Asp	ATA Ile	TTA Leu	CAA Gln	ATT Ile	GGC Gly	TGG Trp	TGG Trp	GCC Ala	2836
	920					925					930					
ACT Thr	GCT Ala	GCT Ala	GCC Ala	TGG Trp	TCT Ser	ATT Ile	CTA Leu	CAG Gln	CAG Gln	TTT Phe	CTC Leu	TTG Leu	AGT Ser	TTG Leu	ACC Thr	2884
935					940					945					950	
TTT Phe	CCA Pro	CGA Arg	CTC Leu	CTT Leu	GAG Glu	GCA Ala	GTT Val	GAG Glu	ATG Met	GAG Glu	GAT Asp	GAT Asp	GAC Asp	TTC Phe	ACG Thr	2932
				955					960					965		
GCC Ala	TCC Ser	CTG Leu	TCC Ser	AAG Lys	CAG Gln	AGC Ser	TGC Cys	ATT Ile	ACT Thr	GAA Glu	CAA Gln	ACC Thr	CAG Gln	TAT Tyr	TTC Phe	2980
			970					975					980			

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TTC GAT AAC GAC AGT AAA TCA TTC AGT GGT GTA TTA GAC TGT GGA AAC Phe Asp Asn Asp Ser Lys Ser Phe Ser Gly Val Leu Asp Cys Gly Asn 985 990 995	3028
TGT TCC AGA ATC TTT CAT GGA GAA AAG CTT ATG AAC ACC AAC TTA ATA Cys Ser Arg Ile Phe His Gly Glu Lys Leu Met Asn Thr Asn Leu Ile 1000 1005 1010	3076
TTC ATA ATG GTT GAG AGC AAA GGG ACA TGT CCA TGT GAC ACA CGA CTG Phe Ile Met Val Glu Ser Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu 1015 1020 1025 1030	3124
CTC ATA CAA GCG GAG CAG ACT TCT GAC GGT CCA AAT CCT TGT GAC ATG Leu Ile Gln Ala Glu Gln Thr Ser Asp Gly Pro Asn Pro Cys Asp Met 1035 1040 1045	3172
GTT AAG CAA CCT AGA TAC CGA AAA GGG CCT GAT GTC TGC TTT GAT AAC Val Lys Gln Pro Arg Tyr Arg Lys Gly Pro Asp Val Cys Phe Asp Asn 1050 1055 1060	3220
AAT GTC TTG GAG GAT TAT ACT GAC TGT GGT GGT GTT TCT GGA TTA AAT Asn Val Leu Glu Asp Tyr Thr Asp Cys Gly Gly Val Ser Gly Leu Asn 1065 1070 1075	3268
CCC TCC CTG TGG TAT ATC ATT GGA ATC CAG TTT CTA CTA CTT TGG CTG Pro Ser Leu Trp Tyr Ile Ile Gly Ile Gln Phe Leu Leu Leu Trp Leu 1080 1085 1090	3316
GTA TCT GGC AGC ACA CAC CGG CTG TTA TGACCTTCTA AAAACCAAAT Val Ser Gly Ser Thr His Arg Leu Leu 1095 1100	3363
CTGCATAGTT AAACCTCCAGA CCCTGCCAAA ACATGAGCCC TGCCCTCAAT TACAGTAACG	3423
TAGGGTCAGC TATAAAATCA GACAAACATT AGCTGGGCCT GTTCCATGGC ATAACACTAA	3483
GGCGCAGACT CCTAAGGCAC CCACTGGCTG CATGTCAGGG TGTCAGATCC TTAAACGTGT	3543
GTGAATGCTG CATCATCTAT GTGTAACATC AAAGCAAAAT CCTATACGTG TCCTCTATTG	3603
GAAAATTTGG GCGTTTGTG TTGCATTGTT GGT	3636

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3585 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 35..3295

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(D) OTHER INFORMATION: /standard_name= "Alpha-2c"

(ix) FEATURE:

(A) NAME/KEY: 5'UTR

(B) LOCATION: 1..34

(ix) FEATURE:

(A) NAME/KEY: 3'UTR

(B) LOCATION: 3296..3585

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GCGGGGGAGG GGGCATTGAT CTTGATCGC GAAG ATG GCT GCT GGC TGC CTG	52
Met Ala Ala Gly Cys Leu	
1 5	
CTG GCC TTG ACT CTG ACA CTT TTC CAA TCT TTG CTC ATC GGC CCC TCG	100
Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser Leu Leu Ile Gly Pro Ser	
10 15 20	
TCG GAG GAG CCG TTC CCT TCG GCC GTC ACT ATC AAA TCA TGG GTG GAT	148
Ser Glu Glu Pro Phe Pro Ser Ala Val Thr Ile Lys Ser Trp Val Asp	
25 30 35	
AAG ATG CAA GAA GAC CTT GTC ACA CTG GCA AAA ACA GCA AGT GGA GTC	196
Lys Met Gln Glu Asp Leu Val Thr Leu Ala Lys Thr Ala Ser Gly Val	
40 45 50	
AAT CAG CTT GTT GAT ATT TAT GAG AAA TAT CAA GAT TTG TAT ACT GTG	244
Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr Gln Asp Leu Tyr Thr Val	
55 60 65 70	
GAA CCA AAT AAT GCA CGC CAG CTG GTA GAA ATT GCA GCC AGG GAT ATT	292
Glu Pro Asn Asn Ala Arg Gln Leu Val Glu Ile Ala Ala Arg Asp Ile	
75 80 85	
GAG AAA CTT CTG AGC AAC AGA TCT AAA GCC CTG GTG AGC CTG GCA TTG	340
Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala Leu Val Ser Leu Ala Leu	
90 95 100	
GAA GCG GAG AAA GTT CAA GCA GCT CAC CAG TGG AGA GAA GAT TTT GCA	388
Glu Ala Glu Lys Val Gln Ala Ala His Gln Trp Arg Glu Asp Phe Ala	
105 110 115	
AGC AAT GAA GTT GTC TAC TAC AAT GCA AAG GAT GAT CTC GAT CCT GAG	436
Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys Asp Asp Leu Asp Pro Glu	
120 125 130	
AAA AAT GAC AGT GAG CCA GGC AGC CAG AGG ATA AAA CCT GTT TTC ATT	484
Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg Ile Lys Pro Val Phe Ile	
135 140 145 150	
GAA GAT GCT AAT TTT GGA CGA CAA ATA TCT TAT CAG CAC GCA GCA GTC	532
Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser Tyr Gln His Ala Ala Val	
155 160 165	

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CAT	ATT	CCT	ACT	GAC	ATC	TAT	GAG	GGC	TCA	ACA	ATT	GTG	TTA	AAT	GAA	580
His	Ile	Pro	Thr	Asp	Ile	Tyr	Glu	Gly	Ser	Thr	Ile	Val	Leu	Asn	Glu	
			170					175					180			
CTC	AAC	TGG	ACA	AGT	GCC	TTA	GAT	GAA	GTT	TTC	AAA	AAG	AAT	CGC	GAG	628
Leu	Asn	Trp	Thr	Ser	Ala	Leu	Asp	Glu	Val	Phe	Lys	Lys	Asn	Arg	Glu	
		185					190					195				
GAA	GAC	CCT	TCA	TTA	TTG	TGG	CAG	GTT	TTT	GGC	AGT	GCC	ACT	GGC	CTA	676
Glu	Asp	Pro	Ser	Leu	Leu	Trp	Gln	Val	Phe	Gly	Ser	Ala	Thr	Gly	Leu	
	200					205					210					
GCT	CGA	TAT	TAT	CCA	GCT	TCA	CCA	TGG	GTT	GAT	AAT	AGT	AGA	ACT	CCA	724
Ala	Arg	Tyr	Tyr	Pro	Ala	Ser	Pro	Trp	Val	Asp	Asn	Ser	Arg	Thr	Pro	
215					220					225					230	
AAT	AAG	ATT	GAC	CTT	TAT	GAT	GTA	CGC	AGA	AGA	CCA	TGG	TAC	ATC	CAA	772
Asn	Lys	Ile	Asp	Leu	Tyr	Asp	Val	Arg	Arg	Arg	Pro	Trp	Tyr	Ile	Gln	
			235					240						245		
GGA	GCT	GCA	TCT	CCT	AAA	GAC	ATG	CTT	ATT	CTG	GTG	GAT	GTG	AGT	GGA	820
Gly	Ala	Ala	Ser	Pro	Lys	Asp	Met	Leu	Ile	Leu	Val	Asp	Val	Ser	Gly	
			250					255					260			
AGT	GTT	AGT	GGA	TTG	ACA	CTT	AAA	CTG	ATC	CGA	ACA	TCT	GTC	TCC	GAA	868
Ser	Val	Ser	Gly	Leu	Thr	Leu	Lys	Leu	Ile	Arg	Thr	Ser	Val	Ser	Glu	
		265					270					275				
ATG	TTA	GAA	ACC	CTC	TCA	GAT	GAT	GAT	TTC	GTG	AAT	GTA	GCT	TCA	TTT	916
Met	Leu	Glu	Thr	Leu	Ser	Asp	Asp	Asp	Phe	Val	Asn	Val	Ala	Ser	Phe	
	280					285					290					
AAC	AGC	AAT	GCT	CAG	GAT	GTA	AGC	TGT	TTT	CAG	CAC	CTT	GTC	CAA	GCA	964
Asn	Ser	Asn	Ala	Gln	Asp	Val	Ser	Cys	Phe	Gln	His	Leu	Val	Gln	Ala	
295					300					305					310	
AAT	GTA	AGA	AAT	AAA	AAA	GTG	TTG	AAA	GAC	GCG	GTG	AAT	AAT	ATC	ACA	1012
Asn	Val	Arg	Asn	Lys	Lys	Val	Leu	Lys	Asp	Ala	Val	Asn	Asn	Ile	Thr	
			315						320					325		
GCC	AAA	GGA	ATT	ACA	GAT	TAT	AAG	AAG	GGC	TTT	AGT	TTT	GCT	TTT	GAA	1060
Ala	Lys	Gly	Ile	Thr	Asp	Tyr	Lys	Lys	Gly	Phe	Ser	Phe	Ala	Phe	Glu	
			330					335					340			
CAG	CTG	CTT	AAT	TAT	AAT	GTT	TCC	AGA	GCA	AAC	TGC	AAT	AAG	ATT	ATT	1108
Gln	Leu	Leu	Asn	Tyr	Asn	Val	Ser	Arg	Ala	Asn	Cys	Asn	Lys	Ile	Ile	
		345					350					355				
ATG	CTA	TTC	ACG	GAT	GGA	GGA	GAA	GAG	AGA	GCC	CAG	GAG	ATA	TTT	AAC	1156
Met	Leu	Phe	Thr	Asp	Gly	Gly	Glu	Glu	Arg	Ala	Gln	Glu	Ile	Phe	Asn	
	360					365					370					
AAA	TAC	AAT	AAA	GAT	AAA	AAA	GTA	CGT	GTA	TTC	AGG	TTT	TCA	GTT	GGT	1204
Lys	Tyr	Asn	Lys	Asp	Lys	Lys	Val	Arg	Val	Phe	Arg	Phe	Ser	Val	Gly	
375					380					385					390	

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CAA	CAC	AAT	TAT	GAG	AGA	GGA	CCT	ATT	CAG	TGG	ATG	GCC	TGT	GAA	AAC	1252
Gln	His	Asn	Tyr	Glu	Arg	Gly	Pro	Ile	Gln	Trp	Met	Ala	Cys	Glu	Asn	
				395					400					405		
AAA	GGT	TAT	TAT	TAT	GAA	ATT	CCT	TCC	ATT	GGT	GCA	ATA	AGA	ATC	AAT	1300
Lys	Gly	Tyr	Tyr	Tyr	Glu	Ile	Pro	Ser	Ile	Gly	Ala	Ile	Arg	Ile	Asn	
			410					415					420			
ACT	CAG	GAA	TAT	TTG	GAT	GTT	TTG	GGA	AGA	CCA	ATG	GTT	TTA	GCA	GGA	1348
Thr	Gln	Glu	Tyr	Leu	Asp	Val	Leu	Gly	Arg	Pro	Met	Val	Leu	Ala	Gly	
			425				430					435				
GAC	AAA	GCT	AAG	CAA	GTC	CAA	TGG	ACA	AAT	GTG	TAC	CTG	GAT	GCA	TTG	1396
Asp	Lys	Ala	Lys	Gln	Val	Gln	Trp	Thr	Asn	Val	Tyr	Leu	Asp	Ala	Leu	
	440					445					450					
GAA	CTG	GGA	CTT	GTC	ATT	ACT	GGA	ACT	CTT	CCG	GTC	TTC	AAC	ATA	ACC	1444
Glu	Leu	Gly	Leu	Val	Ile	Thr	Gly	Thr	Leu	Pro	Val	Phe	Asn	Ile	Thr	
	455				460					465					470	
GGC	CAA	TTT	GAA	AAT	AAG	ACA	AAC	TTA	AAG	AAC	CAG	CTG	ATT	CTT	GGT	1492
Gly	Gln	Phe	Glu	Asn	Lys	Thr	Asn	Leu	Lys	Asn	Gln	Leu	Ile	Leu	Gly	
				475					480					485		
GTG	ATG	GGA	GTA	GAT	GTG	TCT	TTG	GAA	GAT	ATT	AAA	AGA	CTG	ACA	CCA	1540
Val	Met	Gly	Val	Asp	Val	Ser	Leu	Glu	Asp	Ile	Lys	Arg	Leu	Thr	Pro	
			490					495					500			
CGT	TTT	ACA	CTG	TGC	CCC	AAT	GGG	TAT	TAC	TTT	GCA	ATC	GAT	CCT	AAT	1588
Arg	Phe	Thr	Leu	Cys	Pro	Asn	Gly	Tyr	Tyr	Phe	Ala	Ile	Asp	Pro	Asn	
		505					510					515				
GGT	TAT	GTT	TTA	TTA	CAT	CCA	AAT	CTT	CAG	CCA	AAG	GAG	CCA	GTA	ACA	1636
Gly	Tyr	Val	Leu	Leu	His	Pro	Asn	Leu	Gln	Pro	Lys	Glu	Pro	Val	Thr	
			520				525					530				
TTG	GAT	TTC	CTT	GAT	GCA	GAG	TTA	GAG	AAT	GAT	ATT	AAA	GTG	GAG	ATT	1684
Leu	Asp	Phe	Leu	Asp	Ala	Glu	Leu	Glu	Asn	Asp	Ile	Lys	Val	Glu	Ile	
					540					545					550	
CGA	AAT	AAG	ATG	ATT	GAT	GGG	GAA	AGT	GGA	GAA	AAA	ACA	TTC	AGA	ACT	1732
Arg	Asn	Lys	Met	Ile	Asp	Gly	Glu	Ser	Gly	Glu	Lys	Thr	Phe	Arg	Thr	
				555					560					565		
CTG	GTT	AAA	TCT	CAA	GAT	GAG	AGA	TAT	ATT	GAC	AAA	GGA	AAC	AGG	ACA	1780
Leu	Val	Lys	Ser	Gln	Asp	Glu	Arg	Tyr	Ile	Asp	Lys	Gly	Asn	Arg	Thr	
				570				575					580			
TAC	ACA	TGG	ACA	CCT	GTC	AAT	GGC	ACA	GAT	TAC	AGT	TTG	GCC	TTG	GTA	1828
Tyr	Thr	Trp	Thr	Pro	Val	Asn	Gly	Thr	Asp	Tyr	Ser	Leu	Ala	Leu	Val	
			585				590					595				
TTA	CCA	ACC	TAC	AGT	TTT	TAC	TAT	ATA	AAA	GCC	AAA	CTA	GAA	GAG	ACA	1876
Leu	Pro	Thr	Tyr	Ser	Phe	Tyr	Tyr	Ile	Lys	Ala	Lys	Leu	Glu	Glu	Thr	
			600				605					610				

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ATA Ile 615	ACT Thr	CAG Gln	GCC Ala	AGA Arg	TCA Ser	AAA Lys	AAG Lys	GGC Gly	AAA Lys	ATG Met	AAG Lys	GAT Asp	TCG Ser	GAA Glu	ACC Thr	1924
CTG Leu	AAG Lys	CCA Pro	GAT Asp	AAT Asn	TTT Phe	GAA Glu	GAA Glu	TCT Ser	GGC Gly	TAT Tyr	ACA Thr	TTC Phe	ATA Ile	GCA Ala	CCA Pro	1972
AGA Arg	GAT Asp	TAC Tyr	TGC Cys	AAT Asn	GAC Asp	CTG Leu	AAA Lys	ATA Ile	TCG Ser	GAT Asp	AAT Asn	AAC Asn	ACT Thr	GAA Glu	TTT Phe	2020
CTT Leu	TTA Leu	AAT Asn	TTC Phe	AAC Asn	GAG Glu	TTT Phe	ATT Ile	GAT Asp	AGA Arg	AAA Lys	ACT Thr	CCA Pro	AAC Asn	AAC Asn	CCA Pro	2068
TCA Ser	TGT Cys	AAC Asn	GCG Ala	GAT Asp	TTG Leu	ATT Ile	AAT Asn	AGA Arg	GTC Val	TTG Leu	CTT Leu	GAT Asp	GCA Ala	GGC Gly	TTT Phe	2116
ACA Thr	AAT Asn	GAA Glu	CTT Leu	GTC Val	CAA Gln	AAT Asn	TAC Tyr	TGG Trp	AGT Ser	AAG Lys	CAG Gln	AAA Lys	AAT Asn	ATC Ile	AAG Lys	2164
GGA Gly	GTG Val	AAA Lys	GCA Ala	CGA Arg	TTT Phe	GTT Val	GTG Val	ACT Thr	GAT Asp	GGT Gly	GGG Gly	ATT Ile	ACC Thr	AGA Arg	GTT Val	2212
TAT Tyr	CCC Pro	AAA Lys	GAG Glu	GCT Ala	GGA Gly	GAA Glu	AAT Asn	TGG Trp	CAA Gln	GAA Glu	AAC Asn	CCA Pro	GAG Glu	ACA Thr	TAT Tyr	2260
GAG Glu	GAC Asp	AGC Ser	TTC Phe	TAT Tyr	AAA Lys	AGG Arg	AGC Ser	CTA Leu	GAT Asp	AAT Asn	GAT Asp	AAC Asn	TAT Tyr	GTT Val	TTC Phe	2308
ACT Thr	GCT Ala	CCC Pro	TAC Tyr	TTT Phe	AAC Asn	AAA Lys	AGT Ser	GGA Gly	CCT Pro	GGT Gly	GCC Ala	TAT Tyr	GAA Glu	TCG Ser	GGC Gly	2356
ATT Ile	ATG Met	GTA Val	AGC Ser	AAA Lys	GCT Ala	GTA Val	GAA Glu	ATA Ile	TAT Tyr	ATT Ile	CAA Gln	GGG Gly	AAA Lys	CTT Leu	CTT Leu	2404
AAA Lys	CCT Pro	GCA Ala	GTT Val	GTT Val	GGA Gly	ATT Ile	AAA Lys	ATT Ile	GAT Asp	GTA Val	AAT Asn	TCC Ser	TGG Trp	ATA Ile	GAG Glu	2452
AAT Asn	TTC Phe	ACC Thr	AAA Lys	ACC Thr	TCA Ser	ATC Ile	AGA Arg	GAT Asp	CCG Pro	TGT Cys	GCT Ala	GGT Gly	CCA Pro	GTT Val	TGT Cys	2500
GAC Asp	TGC Cys	AAA Lys	AGA Arg	AAC Asn	AGT Ser	GAC Asp	GTA Val	ATG Met	GAT Asp	TGT Cys	GTG Val	ATT Ile	CTG Leu	GAT Asp	GAT Asp	2548

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GGT	GGG	TTT	CTT	CTG	ATG	GCA	AAT	CAT	GAT	GAT	TAT	ACT	AAT	CAG	ATT	2596
Gly	Gly	Phe	Leu	Leu	Met	Ala	Asn	His	Asp	Asp	Tyr	Thr	Asn	Gln	Ile	
	840					845					850					
GGA	AGA	TTT	TTT	GGA	GAG	ATT	GAT	CCC	AGC	TTG	ATG	AGA	CAC	CTG	GTT	2644
Gly	Arg	Phe	Phe	Gly	Glu	Ile	Asp	Pro	Ser	Leu	Met	Arg	His	Leu	Val	
855				860						865					870	
AAT	ATA	TCA	GTT	TAT	GCT	TTT	AAC	AAA	TCT	TAT	GAT	TAT	CAG	TCA	GTA	2692
Asn	Ile	Ser	Val	Tyr	Ala	Phe	Asn	Lys	Ser	Tyr	Asp	Tyr	Gln	Ser	Val	
			875						880				885			
TGT	GAG	CCC	GGT	GCT	GCA	CCA	AAA	CAA	GGA	GCA	GGA	CAT	CGC	TCA	GCA	2740
Cys	Glu	Pro	Gly	Ala	Ala	Pro	Lys	Gln	Gly	Ala	Gly	His	Arg	Ser	Ala	
			890					895					900			
TAT	GTG	CCA	TCA	GTA	GCA	GAC	ATA	TTA	CAA	ATT	GGC	TGG	TGG	GCC	ACT	2788
Tyr	Val	Pro	Ser	Val	Ala	Asp	Ile	Leu	Gln	Ile	Gly	Trp	Trp	Ala	Thr	
		905					910					915				
GCT	GCT	GCC	TGG	TCT	ATT	CTA	CAG	CAG	TTT	CTC	TTG	AGT	TTG	ACC	TTT	2836
Ala	Ala	Ala	Trp	Ser	Ile	Leu	Gln	Gln	Phe	Leu	Ser	Ser	Leu	Thr	Phe	
	920					925					930					
CCA	CGA	CTC	CTT	GAG	GCA	GTT	GAG	ATG	GAG	GAT	GAT	GAC	TTC	ACG	GCC	2884
Pro	Arg	Leu	Leu	Glu	Ala	Val	Glu	Met	Glu	Asp	Asp	Asp	Phe	Thr	Ala	
935					940					945					950	
TCC	CTG	TCC	AAG	CAG	AGC	TGC	ATT	ACT	GAA	CAA	ACC	CAG	TAT	TTC	TTC	2932
Ser	Leu	Ser	Lys	Gln	Ser	Cys	Ile	Thr	Glu	Gln	Thr	Gln	Tyr	Phe	Phe	
			955						960					965		
GAT	AAC	GAC	AGT	AAA	TCA	TTC	AGT	GGT	GTA	TTA	GAC	TGT	GGA	AAC	TGT	2980
Asp	Asn	Asp	Ser	Lys	Ser	Phe	Ser	Gly	Val	Leu	Asp	Cys	Gly	Asn	Cys	
			970					975					980			
TCC	AGA	ATC	TTT	CAT	GGA	GAA	AAG	CTT	ATG	AAC	ACC	AAC	TTA	ATA	TTC	3028
Ser	Arg	Ile	Phe	His	Gly	Glu	Lys	Leu	Met	Asn	Thr	Asn	Leu	Ile	Phe	
		985					990					995				
ATA	ATG	GTT	GAG	AGC	AAA	GGG	ACA	TGT	CCA	TGT	GAC	ACA	CGA	CTG	CTC	3076
Ile	Met	Val	Glu	Ser	Lys	Gly	Thr	Cys	Pro	Cys	Asp	Thr	Arg	Leu	Leu	
	1000					1005					1010					
ATA	CAA	GCG	GAG	CAG	ACT	TCT	GAC	GGT	CCA	AAT	CCT	TGT	GAC	ATG	GTT	3124
Ile	Gln	Ala	Glu	Gln	Thr	Ser	Asp	Gly	Pro	Asn	Pro	Cys	Asp	Met	Val	
	1015				1020					1025					1030	
AAG	CAA	CCT	AGA	TAC	CGA	AAA	GGG	CCT	GAT	GTC	TGC	TTT	GAT	AAC	AAT	3172
Lys	Gln	Pro	Arg	Tyr	Arg	Lys	Gly	Pro	Asp	Val	Cys	Phe	Asp	Asn	Asn	
			1035						1040					1045		
GTC	TTG	GAG	GAT	TAT	ACT	GAC	TGT	GGT	GGT	GTT	TCT	GGA	TTA	AAT	CCC	3220
Val	Leu	Glu	Asp	Tyr	Thr	Asp	Cys	Gly	Gly	Val	Ser	Gly	Leu	Asn	Pro	
			1050					1055					1060			
TCC	CTG	TGG	TAT	ATC	ATT	GGA	ATC	CAG	TTT	CTA	CTA	CTT	TGG	CTG	GTA	3268

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Ser Leu Trp Tyr Ile Ile Gly Ile Gln Phe Leu Leu Leu Trp Leu Val
 1065 1070 1075

TCT GGC AGC ACA CAC CGG CTG TTA TGACCTTCTA AAAACCAAAT CTGCATAGTT 3322
 Ser Gly Ser Thr His Arg Leu Leu
 1080 1085

AAACTCCAGA CCCTGCCAAA ACATGAGCCC TGCCCTCAAT TACAGTAACG TAGGGTCAGC 3382
 TATAAAATCA GACAAACATT AGCTGGGCCT GTTCCATGGC ATAACACTAA GCGCGAGACT 3442
 CCTAAGGCAC CCACTGGCTG CATGTCAGGG TGTCAGATCC TTAAACGTGT GTGAATGCTG 3505
 CATCATCTAT GTGTAACATC AAAGCAAAT CCTATACGTG TCCTCTATTG GAAAATTG 3562
 GCGTTTGTG TTGCATTGTT GGT 3585

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3564 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 35..3374 (Δ1625 to 1639 & Δ1908 to 1928)
- (D) OTHER INFORMATION: /standard_name= "Alpha-2d"

(ix) FEATURE:

- (A) NAME/KEY: 5'UTR
- (B) LOCATION: 1..34

(ix) FEATURE:

- (A) NAME/KEY: 3'UTR
- (B) LOCATION: 3375..3565

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GCGGGGGAGG GGGCATTGAT CTTGATCGC GAAG ATG GCT GCT GGC TGC CTG 52
 Met Ala Ala Gly Cys Leu
 1 5

CTG GCC TTG ACT CTG ACA CTT TTC CAA TCT TTG CTC ATC GGC CCC TCG 100
 Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser Leu Leu Ile Gly Pro Ser
 10 15 20

TCG GAG GAG CCG TTC CCT TCG GCC GTC ACT ATC AAA TCA TGG GTG GAT 148
 Ser Glu Glu Pro Phe Pro Ser Ala Val Thr Ile Lys Ser Trp Val Asp
 25 30 35

AAG ATG CAA GAA GAC CTT GTC ACA CTG GCA AAA ACA GCA AGT GGA GTC 196
 Lys Met Gln Glu Asp Leu Val Thr Leu Ala Lys Thr Ala Ser Gly Val

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40	45	50	
AAT CAG CTT GTT GAT ATT TAT GAG AAA TAT CAA GAT TTG TAT ACT GTG Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr Gln Asp Leu Tyr Thr Val 55 60 65 70			244
GAA CCA AAT AAT GCA CGC CAG CTG GTA GAA ATT GCA GCC AGG GAT ATT Glu Pro Asn Asn Ala Arg Gln Leu Val Glu Ile Ala Ala Arg Asp Ile 75 80 85			292
GAG AAA CTT CTG AGC AAC AGA TCT AAA GCC CTG GTG AGC CTG GCA TTG Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala Leu Val Ser Leu Ala Leu 90 95 100			340
GAA GCG GAG AAA GTT CAA GCA GCT CAC CAG TGG AGA GAA GAT TTT GCA Glu Ala Glu Lys Val Gln Ala Ala His Gln Trp Arg Glu Asp Phe Ala 105 110 115			388
AGC AAT GAA GTT GTC TAC TAC AAT GCA AAG GAT GAT CTC GAT CCT GAG Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys Asp Asp Leu Asp Pro Glu 120 125 130			436
AAA AAT GAC AGT GAG CCA GGC AGC CAG AGG ATA AAA CCT GTT TTC ATT Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg Ile Lys Pro Val Phe Ile 135 140 145 150			484
GAA GAT GCT AAT TTT GGA CGA CAA ATA TCT TAT CAG CAC GCA GCA GTC Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser Tyr Gln His Ala Ala Val 155 160 165			532
CAT ATT CCT ACT GAC ATC TAT GAG GGC TCA ACA ATT GTG TTA AAT GAA His Ile Pro Thr Asp Ile Tyr Glu Gly Ser Thr Ile Val Leu Asn Glu 170 175 180			580
CTC AAC TGG ACA AGT GCC TTA GAT GAA GTT TTC AAA AAG AAT CGC GAG Leu Asn Trp Thr Ser Ala Leu Asp Glu Val Phe Lys Lys Asn Arg Glu 185 190 195			628
GAA GAC CCT TCA TTA TTG TGG CAG GTT TTT GGC AGT GCC ACT GGC CTA Glu Asp Pro Ser Leu Leu Trp Gln Val Phe Gly Ser Ala Thr Gly Leu 200 205 210			676
GCT CGA TAT TAT CCA GCT TCA CCA TGG GTT GAT AAT AGT AGA ACT CCA Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val Asp Asn Ser Arg Thr Pro 215 220 225 230			724
AAT AAG ATT GAC CTT TAT GAT GTA CGC AGA AGA CCA TGG TAC ATC CAA Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg Arg Pro Trp Tyr Ile Gln 235 240 245			772
GGA GCT GCA TCT CCT AAA GAC ATG CTT ATT CTG GTG GAT GTG AGT GGA Gly Ala Ala Ser Pro Lys Asp Met Leu Ile Leu Val Asp Val Ser Gly 250 255 260			820
AGT GTT AGT GGA TTG ACA CTT AAA CTG ATC CGA ACA TCT GTC TCC GAA Ser Val Ser Gly Leu Thr Leu Lys Leu Ile Arg Thr Ser Val Ser Glu 265 270 275 280			868

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265					270					275						
ATG	TTA	GAA	ACC	CTC	TCA	GAT	GAT	GAT	TTC	GTG	AAT	GTA	GCT	TCA	TTT	916
Met	Leu	Glu	Thr	Leu	Ser	Asp	Asp	Asp	Phe	Val	Asn	Val	Ala	Ser	Phe	
	280					285					290					
AAC	AGC	AAT	GCT	CAG	GAT	GTA	AGC	TGT	TTT	CAG	CAC	CTT	GTC	CAA	GCA	964
Asn	Ser	Asn	Ala	Gln	Asp	Val	Ser	Cys	Phe	Gln	His	Leu	Val	Gln	Ala	
295					300					305					310	
AAT	GTA	AGA	AAT	AAA	AAA	GTG	TTG	AAA	GAC	GCG	GTG	AAT	AAT	ATC	ACA	1012
Asn	Val	Arg	Asn	Lys	Lys	Val	Leu	Lys	Asp	Ala	Val	Asn	Asn	Ile	Thr	
				315					320					325		
GCC	AAA	GGA	ATT	ACA	GAT	TAT	AAG	AAG	GGC	TTT	AGT	TTT	GCT	TTT	GAA	1060
Ala	Lys	Gly	Ile	Thr	Asp	Tyr	Lys	Lys	Gly	Phe	Ser	Phe	Ala	Phe	Glu	
			330					335					340			
CAG	CTG	CTT	AAT	TAT	AAT	GTT	TCC	AGA	GCA	AAC	TGC	AAT	AAG	ATT	ATT	1108
Gln	Leu	Leu	Asn	Tyr	Asn	Val	Ser	Arg	Ala	Asn	Cys	Asn	Lys	Ile	Ile	
		345					350					355				
ATG	CTA	TTC	ACG	GAT	GGA	GGA	GAA	GAG	AGA	GCC	CAG	GAG	ATA	TTT	AAC	1156
Met	Leu	Phe	Thr	Asp	Gly	Gly	Glu	Glu	Arg	Ala	Gln	Glu	Ile	Phe	Asn	
	360					365					370					
AAA	TAC	AAT	AAA	GAT	AAA	AAA	GTA	CGT	GTA	TTC	AGG	TTT	TCA	GTT	GGT	1204
Lys	Tyr	Asn	Lys	Asp	Lys	Lys	Val	Arg	Val	Phe	Arg	Phe	Ser	Val	Gly	
375				380						385					390	
CAA	CAC	AAT	TAT	GAG	AGA	GGA	CCT	ATT	CAG	TGG	ATG	GCC	TGT	GAA	AAC	1252
Gln	His	Asn	Tyr	Glu	Arg	Gly	Pro	Ile	Gln	Trp	Met	Ala	Cys	Glu	Asn	
				395					400					405		
AAA	GGT	TAT	TAT	TAT	GAA	ATT	CCT	TCC	ATT	GGT	GCA	ATA	AGA	ATC	AAT	1300
Lys	Gly	Tyr	Tyr	Tyr	Glu	Ile	Pro	Ser	Ile	Gly	Ala	Ile	Arg	Ile	Asn	
			410				415					420				
ACT	CAG	GAA	TAT	TTG	GAT	GTT	TTG	GGA	AGA	CCA	ATG	GTT	TTA	GCA	GGA	1348
Thr	Gln	Glu	Tyr	Leu	Asp	Val	Leu	Gly	Arg	Pro	Met	Val	Leu	Ala	Gly	
		425					430					435				
GAC	AAA	GCT	AAG	CAA	GTC	CAA	TGG	ACA	AAT	GTG	TAC	CTG	GAT	GCA	TTG	1396
Asp	Lys	Ala	Lys	Gln	Val	Gln	Trp	Thr	Asn	Val	Tyr	Leu	Asp	Ala	Leu	
	440					445					450					
GAA	CTG	GGA	CTT	GTC	ATT	ACT	GGA	ACT	CTT	CCG	GTC	TTC	AAC	ATA	ACC	1444
Glu	Leu	Gly	Leu	Val	Ile	Thr	Gly	Thr	Leu	Pro	Val	Phe	Asn	Ile	Thr	
455				460						465					470	
GGC	CAA	TTT	GAA	AAT	AAG	ACA	AAC	TTA	AAG	AAC	CAG	CTG	ATT	CTT	GGT	1492
Gly	Gln	Phe	Glu	Asn	Lys	Thr	Asn	Leu	Lys	Asn	Gln	Leu	Ile	Leu	Gly	
				475				480					485			
GTG	ATG	GGA	GTA	GAT	GTG	TCT	TTG	GAA	GAT	ATT	AAA	AGA	CTG	ACA	CCA	1540
Val	Met	Gly	Val	Asp	Val	Ser	Leu	Glu	Asp	Ile	Lys	Arg	Leu	Thr	Pro	
			490					495					500			

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CGT	TTT	ACA	CTG	TGC	CCC	AAT	GGG	TAT	TAC	TTT	GCA	ATC	GAT	CCT	AAT	1588
Arg	Phe	Thr	Leu	Cys	Pro	Asn	Gly	Tyr	Tyr	Phe	Ala	Ile	Asp	Pro	Asn	
		505					510					515				
GGT	TAT	GTT	TTA	TTA	CAT	CCA	AAT	CTT	CAG	CCA	AAG	GAG	CCA	GTA	ACA	1636
Gly	Tyr	Val	Leu	Leu	His	Pro	Asn	Leu	Gln	Pro	Lys	Glu	Pro	Val	Thr	
	520						525					530				
TTG	GAT	TTC	CTT	GAT	GCA	GAG	TTA	GAG	AAT	GAT	ATT	AAA	GTG	GAG	ATT	1684
Leu	Asp	Phe	Leu	Asp	Ala	Glu	Leu	Glu	Asn	Asp	Ile	Lys	Val	Glu	Ile	
535					540					545					550	
CGA	AAT	AAG	ATG	ATT	GAT	GGG	GAA	AGT	GGA	GAA	AAA	ACA	TTC	AGA	ACT	1732
Arg	Asn	Lys	Met	Ile	Asp	Gly	Glu	Ser	Gly	Glu	Lys	Thr	Phe	Arg	Thr	
				555					560					565		
CTG	GTT	AAA	TCT	CAA	GAT	GAG	AGA	TAT	ATT	GAC	AAA	GGA	AAC	AGG	ACA	1780
Leu	Val	Lys	Ser	Gln	Asp	Glu	Arg	Tyr	Ile	Asp	Lys	Gly	Asn	Arg	Thr	
			570					575					580			
TAC	ACA	TGG	ACA	CCT	GTC	AAT	GGC	ACA	GAT	TAC	AGT	TTG	GCC	TTG	GTA	1828
Tyr	Thr	Trp	Thr	Pro	Val	Asn	Gly	Thr	Asp	Tyr	Ser	Leu	Ala	Leu	Val	
		585					590					595				
TTA	CCA	ACC	TAC	AGT	TTT	TAC	TAT	ATA	AAA	GCC	AAA	CTA	GAA	GAG	ACA	1876
Leu	Pro	Thr	Tyr	Ser	Phe	Tyr	Tyr	Ile	Lys	Ala	Lys	Leu	Glu	Glu	Thr	
	600					605					610					
ATA	ACT	CAG	GCC	AGA	TAT	TCG	GAA	ACC	CTG	AAG	CCA	GAT	AAT	TTT	GAA	1924
Ile	Thr	Gln	Ala	Arg	Tyr	Ser	Glu	Thr	Leu	Lys	Pro	Asp	Asn	Phe	Glu	
615					620					625					630	
GAA	TCT	GGC	TAT	ACA	TTC	ATA	GCA	CCA	AGA	GAT	TAC	TGC	AAT	GAC	CTG	1972
Glu	Ser	Gly	Tyr	Thr	Phe	Ile	Ala	Pro	Arg	Asp	Tyr	Cys	Asn	Asp	Leu	
				635				640						645		
AAA	ATA	TCG	GAT	AAT	AAC	ACT	GAA	TTT	CTT	TTA	AAT	TTC	AAC	GAG	TTT	2020
Lys	Ile	Ser	Asp	Asn	Asn	Thr	Glu	Phe	Leu	Leu	Asn	Phe	Asn	Glu	Phe	
			650					655					660			
ATT	GAT	AGA	AAA	ACT	CCA	AAC	AAC	CCA	TCA	TGT	AAC	GCG	GAT	TTG	ATT	2068
Ile	Asp	Arg	Lys	Thr	Pro	Asn	Asn	Pro	Ser	Cys	Asn	Ala	Asp	Leu	Ile	
		665					670					675				
AAT	AGA	GTC	TTG	CTT	GAT	GCA	GGC	TTT	ACA	AAT	GAA	CTT	GTC	CAA	AAT	2116
Asn	Arg	Val	Leu	Leu	Asp	Ala	Gly	Phe	Thr	Asn	Glu	Leu	Val	Gln	Asn	
		680				685						690				
TAC	TGG	AGT	AAG	CAG	AAA	AAT	ATC	AAG	GGA	GTG	AAA	GCA	CGA	TTT	GTT	2164
Tyr	Trp	Ser	Lys	Gln	Lys	Asn	Ile	Lys	Gly	Val	Lys	Ala	Arg	Phe	Val	
695					700					705					710	
GTG	ACT	GAT	GGT	GGG	ATT	ACC	AGA	GTT	TAT	CCC	AAA	GAG	GCT	GGA	GAA	2212
Val	Thr	Asp	Gly	Gly	Ile	Thr	Arg	Val	Tyr	Pro	Lys	Glu	Ala	Gly	Glu	
				715					720					725		

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AAT	TGG	CAA	GAA	AAC	CCA	GAG	ACA	TAT	GAG	GAC	AGC	TTC	TAT	AAA	AGG	2260
Asn	Trp	Gln	Glu	Asn	Pro	Glu	Thr	Tyr	Glu	Asp	Ser	Phe	Tyr	Lys	Arg	
			730					735					740			
AGC	CTA	GAT	AAT	GAT	AAC	TAT	GTT	TTC	ACT	GCT	CCC	TAC	TTT	AAC	AAA	2308
Ser	Leu	Asp	Asn	Asp	Asn	Tyr	Val	Phe	Thr	Ala	Pro	Tyr	Phe	Asn	Lys	
		745					750					755				
AGT	GGA	CCT	GGT	GCC	TAT	GAA	TCG	GGC	ATT	ATG	GTA	AGC	AAA	GCT	GTA	2356
Ser	Gly	Pro	Gly	Ala	Tyr	Glu	Ser	Gly	Ile	Met	Val	Ser	Lys	Ala	Val	
	760					765					770					
GAA	ATA	TAT	ATT	CAA	GGG	AAA	CTT	CTT	AAA	CCT	GCA	GTT	GTT	GGA	ATT	2404
Glu	Ile	Tyr	Ile	Gln	Gly	Lys	Leu	Leu	Lys	Pro	Ala	Val	Val	Gly	Ile	
	775				780					785					790	
AAA	ATT	GAT	GTA	AAT	TCC	TGG	ATA	GAG	AAT	TTC	ACC	AAA	ACC	TCA	ATC	2452
Lys	Ile	Asp	Val	Asn	Ser	Trp	Ile	Glu	Asn	Phe	Thr	Lys	Thr	Ser	Ile	
				795					800					805		
AGA	GAT	CCG	TGT	GCT	GGT	CCA	GTT	TGT	GAC	TGC	AAA	AGA	AAC	AGT	GAC	2500
Arg	Asp	Pro	Cys	Ala	Gly	Pro	Val	Cys	Asp	Cys	Lys	Arg	Asn	Ser	Asp	
			810					815					820			
GTA	ATG	GAT	TGT	GTG	ATT	CTG	GAT	GAT	GGT	GGG	TTT	CTT	CTG	ATG	GCA	2548
Val	Met	Asp	Cys	Val	Ile	Leu	Asp	Asp	Gly	Gly	Phe	Leu	Leu	Met	Ala	
		825					830					835				
AAT	CAT	GAT	GAT	TAT	ACT	AAT	CAG	ATT	GGA	AGA	TTT	TTT	GGA	GAG	ATT	2596
Asn	His	Asp	Asp	Tyr	Thr	Asn	Gln	Ile	Gly	Arg	Phe	Phe	Gly	Glu	Ile	
	840					845					850					
GAT	CCC	AGC	TTG	ATG	AGA	CAC	CTG	GTT	AAT	ATA	TCA	GTT	TAT	GCT	TTT	2644
Asp	Pro	Ser	Leu	Met	Arg	His	Leu	Val	Asn	Ile	Ser	Val	Tyr	Ala	Phe	
	855				860					865					870	
AAC	AAA	TCT	TAT	GAT	TAT	CAG	TCA	GTA	TGT	GAG	CCC	GGT	GCT	GCA	CCA	2692
Asn	Lys	Ser	Tyr	Asp	Tyr	Gln	Ser	Val	Cys	Glu	Pro	Gly	Ala	Ala	Pro	
				875					880					885		
AAA	CAA	GGA	GCA	GGA	CAT	CGC	TCA	GCA	TAT	GTG	CCA	TCA	GTA	GCA	GAC	2740
Lys	Gln	Gly	Ala	Gly	His	Arg	Ser	Ala	Tyr	Val	Pro	Ser	Val	Ala	Asp	
			890					895					900			
ATA	TTA	CAA	ATT	GGC	TGG	TGG	GCC	ACT	GCT	GCT	GCC	TGG	TCT	ATT	CTA	2788
Ile	Leu	Gln	Ile	Gly	Trp	Trp	Ala	Thr	Ala	Ala	Ala	Trp	Ser	Ile	Leu	
		905					910					915				
CAG	CAG	TTT	CTC	TTG	AGT	TTG	ACC	TTT	CCA	CGA	CTC	CTT	GAG	GCA	GTT	2836
Gln	Gln	Phe	Leu	Leu	Ser	Leu	Thr	Phe	Pro	Arg	Leu	Leu	Glu	Ala	Val	
		920				925					930					
GAG	ATG	GAG	GAT	GAT	GAC	TTC	ACG	GCC	TCC	CTG	TCC	AAG	CAG	AGC	TGC	2884
Glu	Met	Glu	Asp	Asp	Asp	Phe	Thr	Ala	Ser	Leu	Ser	Lys	Gln	Ser	Cys	
	935				940					945					950	
ATT	ACT	GAA	CAA	ACC	CAG	TAT	TTC	TTC	GAT	AAC	GAC	AGT	AAA	TCA	TTC	2932

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Ile	Thr	Glu	Gln	Thr	Gln	Tyr	Phe	Phe	Asp	Asn	Asp	Ser	Lys	Ser	Phe		
				955					960					965			
AGT	GGT	GTA	TTA	GAC	TGT	GGA	AAC	TGT	TCC	AGA	ATC	TTT	CAT	GGA	GAA	2980	
Ser	Gly	Val	Leu	Asp	Cys	Gly	Asn	Cys	Ser	Arg	Ile	Phe	His	Gly	Glu		
			970					975					980				
AAG	CTT	ATG	AAC	ACC	AAC	TTA	ATA	TTC	ATA	ATG	GTT	GAG	AGC	AAA	GGG	3028	
Lys	Leu	Met	Asn	Thr	Asn	Leu	Ile	Phe	Ile	Met	Val	Glu	Ser	Lys	Gly		
		985					990					995					
ACA	TGT	CCA	TGT	GAC	ACA	CGA	CTG	CTC	ATA	CAA	GCG	GAG	CAG	ACT	TCT	3076	
Thr	Cys	Pro	Cys	Asp	Thr	Arg	Leu	Leu	Ile	Gln	Ala	Glu	Gln	Thr	Ser		
	1000					1005					1010						
GAC	GGT	CCA	AAT	CCT	TGT	GAC	ATG	GTT	AAG	CAA	CCT	AGA	TAC	CGA	AAA	3124	
Asp	Gly	Pro	Asn	Pro	Cys	Asp	Met	Val	Lys	Gln	Pro	Arg	Tyr	Arg	Lys		
1015					1020					1025					1030		
GGG	CCT	GAT	GTC	TGC	TTT	GAT	AAC	AAT	GTC	TTG	GAG	GAT	TAT	ACT	GAC	3172	
Gly	Pro	Asp	Val	Cys	Phe	Asp	Asn	Asn	Val	Leu	Glu	Asp	Tyr	Thr	Asp		
			1035						1040					1045			
TGT	GGT	GGT	GTT	TCT	GGA	TTA	AAT	CCC	TCC	CTG	TGG	TAT	ATC	ATT	GGA	3220	
Cys	Gly	Gly	Val	Ser	Gly	Leu	Asn	Pro	Ser	Leu	Trp	Tyr	Ile	Ile	Gly		
			1050					1055					1060				
ATC	CAG	TTT	CTA	CTA	CTT	TGG	CTG	GTA	TCT	GGC	AGC	ACA	CAC	CGG	CTG	3268	
Ile	Gln	Phe	Leu	Leu	Leu	Trp	Leu	Val	Ser	Gly	Ser	Thr	His	Arg	Leu		
		1065					1070					1075					
TTA	TGACCTTCTA	AAAACCAAAT	CTGCATAGTT	AAACTCCAGA	CCCTGCCAAA											3321	
Leu																	
ACATGAGCCC	TGCCCTCAAT	TACAGTAACG	TAGGGTCAGC	TATAAAATCA	GACAAACATT											3381	
AGCTGGGCGCT	GTTCCATGGC	ATAACACTAA	GGCGCAGACT	CCTAAGGCAC	CCACTGGCTG											3441	
CATGTCAGGG	TGTCAGATCC	TTAAACGTGT	GTGAATGCTG	CATCATCTAT	GTGTAACATC											3501	
AAAGCAAAAT	CCTATACGTG	TCCTCTATTG	GAAAATTG	GCGTTTGTTG	TTGCATTGTT											3561	
GGT																3564	

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3579 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

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(A) NAME/KEY: CDS
 (B) LOCATION: 35..3289
 (D) OTHER INFORMATION: /standard_name= "Alpha-2e"

(ix) FEATURE:

(A) NAME/KEY: 5'UTR
 (B) LOCATION: 1..34

(ix) FEATURE:

(A) NAME/KEY: 3'UTR
 (B) LOCATION: 3289..3579

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CGCGGGGAGG GGGCATTGAT CTTTCGATCGC GAAG ATG GCT GCT GGC TGC CTG	52
Met Ala Ala Gly Cys Leu	
1 5	
CTG GCC TTG ACT CTG ACA CTT TTC CAA TCT TTG CTC ATC GGC CCC TCG	100
Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser Leu Leu Ile Gly Pro Ser	
10 15 20	
TCG GAG GAG CCG TTC CCT TCG GCC GTC ACT ATC AAA TCA TGG GTG GAT	148
Ser Glu Glu Pro Phe Pro Ser Ala Val Thr Ile Lys Ser Trp Val Asp	
25 30 35	
AAG ATG CAA GAA GAC CTT GTC ACA CTG GCA AAA ACA GCA AGT GGA GTC	196
Lys Met Gln Glu Asp Leu Val Thr Leu Ala Lys Thr Ala Ser Gly Val	
40 45 50	
AAT CAG CTT GTT GAT ATT TAT GAG AAA TAT CAA GAT TTG TAT ACT GTG	244
Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr Gln Asp Leu Tyr Thr Val	
55 60 65 70	
GAA CCA AAT AAT GCA CGC CAG CTG GTA GAA ATT GCA GCC AGG GAT ATT	292
Glu Pro Asn Asn Ala Arg Gln Leu Val Glu Ile Ala Ala Arg Asp Ile	
75 80 85	
GAG AAA CTT CTG AGC AAC AGA TCT AAA GCC CTG GTG AGC CTG GCA TTG	340
Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala Leu Val Ser Leu Ala Leu	
90 95 100	
GAA GCG GAG AAA GTT CAA GCA GCT CAC CAG TGG AGA GAA GAT TTT GCA	388
Glu Ala Glu Lys Val Gln Ala Ala His Gln Trp Arg Glu Asp Phe Ala	
105 110 115	
AGC AAT GAA GTT GTC TAC TAC AAT GCA AAG GAT GAT CTC GAT CCT GAG	436
Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys Asp Asp Leu Asp Pro Glu	
120 125 130	
AAA AAT GAC AGT GAG CCA GGC AGC CAG AGG ATA AAA CCT GTT TTC ATT	484
Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg Ile Lys Pro Val Phe Ile	
135 140 145 150	
GAA GAT GCT AAT TTT GGA CGA CAA ATA TCT TAT CAG CAC GCA GCA GTC	532

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Glu	Asp	Ala	Asn	Phe 155	Gly	Arg	Gln	Ile	Ser 160	Tyr	Gln	His	Ala	Ala 165	Val		
CAT	ATT	CCT	ACT	GAC	ATC	TAT	GAG	GGC	TCA	ACA	ATT	GTG	TTA	AAT	GAA	580	
His	Ile	Pro	Thr 170	Asp	Ile	Tyr	Glu	Gly 175	Ser	Thr	Ile	Val	Leu 180	Asn	Glu		
CTC	AAC	TGG	ACA	AGT	GCC	TTA	GAT	GAA	GTT	TTC	AAA	AAG	AAT	CGC	GAG	628	
Leu	Asn	Trp 185	Thr	Ser	Ala	Leu	Asp 190	Glu	Val	Phe	Lys	Lys 195	Asn	Arg	Glu		
GAA	GAC	CCT	TCA	TTA	TTG	TGG	CAG	GTT	TTT	GGC	AGT	GCC	ACT	GGC	CTA	676	
Glu	Asp 200	Pro	Ser	Leu	Leu	Trp 205	Gln	Val	Phe	Gly 210	Ser	Ala	Thr	Gly	Leu		
GCT	CGA	TAT	TAT	CCA	GCT	TCA	CCA	TGG	GTT	GAT	AAT	AGT	AGA	ACT	CCA	724	
Ala	Arg	Tyr	Tyr	Pro	Ala 220	Ser	Pro	Trp	Val	Asp 225	Asn	Ser	Arg	Thr	Pro 230		
AAT	AAG	ATT	GAC	CTT	TAT	GAT	GTA	CGC	AGA	AGA	CCA	TGG	TAC	ATC	CAA	772	
Asn	Lys	Ile	Asp	Leu 235	Tyr	Asp	Val	Arg	Arg 240	Arg	Pro	Trp	Tyr	Ile 245	Gln		
GGA	GCT	GCA	TCT	CCT	AAA	GAC	ATG	CTT	ATT	CTG	GTG	GAT	GTG	AGT	GGA	820	
Gly	Ala	Ala	Ser 250	Pro	Lys	Asp	Met 255	Leu	Ile	Leu	Val	Asp 260	Val	Ser	Gly		
AGT	GTT	AGT	GGA	TTG	ACA	CTT	AAA	CTG	ATC	CGA	ACA	TCT	GTC	TCC	GAA	868	
Ser	Val	Ser 265	Gly	Leu	Thr	Leu	Lys 270	Leu	Ile	Arg	Thr	Ser 275	Val	Ser	Glu		
ATG	TTA	GAA	ACC	CTC	TCA	GAT	GAT	GAT	TTC	GTG	AAT	GTA	GCT	TCA	TTT	916	
Met	Leu	Glu	Thr	Leu	Ser	Asp 285	Asp	Asp	Phe	Val	Asn 290	Val	Ala	Ser	Phe		
AAC	AGC	AAT	GCT	CAG	GAT	GTA	AGC	TGT	TTT	CAG	CAC	CTT	GTC	CAA	GCA	964	
Asn	Ser	Asn	Ala	Gln	Asp	Val	Ser	Cys	Phe	Gln 305	His	Leu	Val	Gln 310	Ala		
AAT	GTA	AGA	AAT	AAA	AAA	GTG	TTG	AAA	GAC	GCG	GTG	AAT	AAT	ATC	ACA	1012	
Asn	Val	Arg	Asn	Lys 315	Lys	Val	Leu	Lys	Asp 320	Ala	Val	Asn	Asn	Ile 325	Thr		
GCC	AAA	GGA	ATT	ACA	GAT	TAT	AAG	AAG	GGC	TTT	AGT	TTT	GCT	TTT	GAA	1060	
Ala	Lys	Gly	Ile 330	Thr	Asp	Tyr	Lys	Lys 335	Gly	Phe	Ser	Phe 340	Ala	Phe	Glu		
CAG	CTG	CTT	AAT	TAT	AAT	GTT	TCC	AGA	GCA	AAC	TGC	AAT	AAG	ATT	ATT	1108	
Gln	Leu	Leu 345	Asn	Tyr	Asn	Val	Ser	Arg 350	Ala	Asn	Cys	Asn 355	Lys	Ile	Ile		
ATG	CTA	TTC	ACG	GAT	GGA	GGA	GAA	GAG	AGA	GCC	CAG	GAG	ATA	TTT	AAC	1156	
Met	Leu	Phe	Thr	Asp	Gly	Gly 365	Glu	Glu	Arg	Ala	Gln 370	Glu	Ile	Phe	Asn		
AAA	TAC	AAT	AAA	GAT	AAA	AAA	GTA	CGT	GTA	TTC	AGG	TTT	TCA	GTT	GGT	1204	

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Lys 375	Tyr	Asn	Lys	Asp	Lys 380	Lys	Val	Arg	Val	Phe 385	Arg	Phe	Ser	Val	Gly 390	
CAA	CAC	AAT	TAT	GAG	AGA	GGA	CCT	ATT	CAG	TGG	ATG	GCC	TGT	GAA	AAC	1252
Gln	His	Asn	Tyr	Glu	Arg	Gly	Pro	Ile	Gln	Trp	Met	Ala	Cys	Glu	Asn	
				395					400					405		
AAA	GGT	TAT	TAT	TAT	GAA	ATT	CCT	TCC	ATT	GGT	GCA	ATA	AGA	ATC	AAT	1300
Lys	Gly	Tyr	Tyr	Tyr	Glu	Ile	Pro	Ser	Ile	Gly	Ala	Ile	Arg	Ile	Asn	
			410					415					420			
ACT	CAG	GAA	TAT	TTG	GAT	GTT	TTG	GGA	AGA	CCA	ATG	GTT	TTA	GCA	GGA	1348
Thr	Gln	Glu	Tyr	Leu	Asp	Val	Leu	Gly	Arg	Pro	Met	Val	Leu	Ala	Gly	
		425					430					435				
GAC	AAA	GCT	AAG	CAA	GTC	CAA	TGG	ACA	AAT	GTG	TAC	CTG	GAT	GCA	TTG	1396
Asp	Lys	Ala	Lys	Gln	Val	Gln	Trp	Thr	Asn	Val	Tyr	Leu	Asp	Ala	Leu	
	440					445					450					
GAA	CTG	GGA	CTT	GTC	ATT	ACT	GGA	ACT	CTT	CCG	GTC	TTC	AAC	ATA	ACC	1444
Glu	Leu	Gly	Leu	Val	Ile	Thr	Gly	Thr	Leu	Pro	Val	Phe	Asn	Ile	Thr	
455					460					465					470	
GGC	CAA	TTT	GAA	AAT	AAG	ACA	AAC	TTA	AAG	AAC	CAG	CTG	ATT	CTT	GGT	1492
Gly	Gln	Phe	Glu	Asn	Lys	Thr	Asn	Leu	Lys	Asn	Gln	Leu	Ile	Leu	Gly	
				475					480					485		
GTG	ATG	GGA	GTA	GAT	GTG	TCT	TTG	GAA	GAT	ATT	AAA	AGA	CTG	ACA	CCA	1540
Val	Met	Gly	Val	Asp	Val	Ser	Leu	Glu	Asp	Ile	Lys	Arg	Leu	Thr	Pro	
			490					495					500			
CGT	TTT	ACA	CTG	TGC	CCC	AAT	GGG	TAT	TAC	TTT	GCA	ATC	GAT	CCT	AAT	1588
Arg	Phe	Thr	Leu	Cys	Pro	Asn	Gly	Tyr	Tyr	Phe	Ala	Ile	Asp	Pro	Asn	
		505					510					515				
GGT	TAT	GTT	TTA	TTA	CAT	CCA	AAT	CTT	CAG	CCA	AAG	AAC	CCC	AAA	TCT	1636
Gly	Tyr	Val	Leu	Leu	His	Pro	Asn	Leu	Gln	Pro	Lys	Asn	Pro	Lys	Ser	
	520					525					530					
CAG	GAG	CCA	GTA	ACA	TTG	GAT	TTC	CTT	GAT	GCA	GAG	TTA	GAG	AAT	GAT	1684
Gln	Glu	Pro	Val	Thr	Leu	Asp	Phe	Leu	Asp	Ala	Glu	Leu	Glu	Asn	Asp	
535					540					545					550	
ATT	AAA	GTG	GAG	ATT	CGA	AAT	AAG	ATG	ATT	GAT	GGG	GAA	AGT	GGA	GAA	1732
Ile	Lys	Val	Glu	Ile	Arg	Asn	Lys	Met	Ile	Asp	Gly	Glu	Ser	Gly	Glu	
				555					560					565		
AAA	ACA	TTC	AGA	ACT	CTG	GTT	AAA	TCT	CAA	GAT	GAG	AGA	TAT	ATT	GAC	1780
Lys	Thr	Phe	Arg	Thr	Leu	Val	Lys	Ser	Gln	Asp	Glu	Arg	Tyr	Ile	Asp	
			570					575					580			
AAA	GGA	AAC	AGG	ACA	TAC	ACA	TGG	ACA	CCT	GTC	AAT	GGC	ACA	GAT	TAC	1828
Lys	Gly	Asn	Arg	Thr	Tyr	Thr	Trp	Thr	Pro	Val	Asn	Gly	Thr	Asp	Tyr	
		585					590					595				
AGT	TTG	GCC	TTG	GTA	TTA	CCA	ACC	TAC	AGT	TTT	TAC	TAT	ATA	AAA	GCC	1876

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Ser 600	Leu	Ala	Leu	Val	Leu 605	Pro	Thr	Tyr	Ser	Phe	Tyr 610	Tyr	Ile	Lys	Ala	
AAA Lys 615	CTA Leu	GAA Glu	GAG Glu	ACA Thr	ATA Ile 620	ACT Thr	CAG Gln	GCC Ala	AGA Arg	TAT Tyr 625	TCG Ser	GAA Glu	ACC Thr	CTG Leu 630	AAG Lys 630	1924
CCA Pro	GAT Asp	AAT Asn	TTT Phe	GAA Glu 635	GAA Glu	TCT Ser	GGC Gly	TAT Tyr	ACA Thr 640	TTC Phe	ATA Ile	GCA Ala	CCA Pro	AGA Arg 645	GAT Asp	1972
TAC Tyr	TGC Cys	AAT Asn	GAC Asp 650	CTG Leu	AAA Lys	ATA Ile	TCG Ser	GAT Asp 655	AAT Asn	AAC Asn	ACT Thr	GAA Glu 660	TTT Phe	CTT Leu	TTA Leu	2020
AAT Asn	TTC Phe	AAC Asn 665	GAG Glu	TTT Phe	ATT Ile	GAT Asp	AGA Arg 670	AAA Lys	ACT Thr	CCA Pro	AAC Asn 675	AAC Asn	CCA Pro	TCA Ser	TGT Cys	2068
AAC Asn 680	GCG Ala	GAT Asp	TTG Leu	ATT Ile	AAT Asn 685	AGA Arg	GTC Val	TTG Leu	CTT Leu	GAT Asp 690	GCA Ala	GGC Gly	TTT Phe	ACA Thr	AAT Asn	2116
GAA Glu 695	CTT Leu	GTC Val	CAA Gln	AAT Asn	TAC Tyr 700	TGG Trp	AGT Ser	AAG Lys	CAG Gln 705	AAA Lys	AAT Asn	ATC Ile	AAG Lys	GGA Gly 710	GTG Val 710	2164
AAA Lys	GCA Ala	CGA Arg	TTT Phe	GTT Val 715	GTG Val	ACT Thr	GAT Asp	GGT Gly 720	GGG Gly	ATT Ile	ACC Thr	AGA Arg	GTT Val	TAT Tyr 725	CCC Pro	2212
AAA Lys	GAG Glu	GCT Ala	GGA Gly 730	GAA Glu	AAT Asn	TGG Trp	CAA Gln	GAA Glu 735	AAC Asn	CCA Pro	GAG Glu	ACA Thr	TAT Tyr 740	GAG Glu	GAC Asp	2260
AGC Ser	TTC Phe	TAT Tyr 745	AAA Lys	AGG Arg	AGC Ser	CTA Leu	GAT Asp 750	AAT Asn	GAT Asp	AAC Asn	TAT Tyr 755	GTT Val	TTC Phe	ACT Thr	GCT Ala	2308
CCC Pro	TAC Tyr 760	TTT Phe	AAC Asn	AAA Lys	AGT Ser	GGA Gly 765	CCT Pro	GGT Gly	GCC Ala	TAT Tyr 770	GAA Glu	TCG Ser	GGC Gly	ATT Ile	ATG Met	2356
GTA Val 775	AGC Ser	AAA Lys	GCT Ala	GTA Val	GAA Glu 780	ATA Ile	TAT Tyr	ATT Ile	CAA Gln 785	GGG Gly	AAA Lys	CTT Leu	CTT Leu	AAA Lys	CCT Pro 790	2404
GCA Ala	GTT Val	GTT Val	GGA Gly 795	ATT Ile	AAA Lys	ATT Ile	GAT Asp	GTA Val 800	AAT Asn	TCC Ser	TGG Trp	ATA Ile	GAG Glu	AAT Asn 805	TTC Phe	2452
ACC Thr	AAA Lys	ACC Thr	TCA Ser 810	ATC Ile	AGA Arg	GAT Asp	CCG Pro	TGT Cys 815	GCT Ala	GGT Gly	CCA Pro	GTT Val	TGT Cys 820	GAC Asp	TGC Cys	2500
AAA Ala	AGA Arg	AAC Asn	AGT Glu	GAC Glu	GTA Val	ATG Leu	GAT Asp	TGT Cys	GTG Glu	ATT Ile	CTG Glu	GAT Glu	GGT Glu	GGG Glu		2548

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Lys	Arg	Asn	Ser	Asp	Val	Met	Asp	Cys	Val	Ile	Leu	Asp	Asp	Gly	Gly	
		825					830					835				
TTT	CTT	CTG	ATG	GCA	AAT	CAT	GAT	GAT	TAT	ACT	AAT	CAG	ATT	GGA	AGA	2596
Phe	Leu	Leu	Met	Ala	Asn	His	Asp	Asp	Tyr	Thr	Asn	Gln	Ile	Gly	Arg	
	840					845					850					
TTT	TTT	GGA	GAG	ATT	GAT	CCC	AGC	TTG	ATG	AGA	CAC	CTG	GTT	AAT	ATA	2644
Phe	Phe	Gly	Glu	Ile	Asp	Pro	Ser	Leu	Met	Arg	His	Leu	Val	Asn	Ile	
855					860					865					870	
TCA	GTT	TAT	GCT	TTT	AAC	AAA	TCT	TAT	GAT	TAT	CAG	TCA	GTA	TGT	GAG	2692
Ser	Val	Tyr	Ala	Phe	Asn	Lys	Ser	Tyr	Asp	Tyr	Gln	Ser	Val	Cys	Glu	
				875					880					885		
CCC	GGT	GCT	GCA	CCA	AAA	CAA	GGA	GCA	GGA	CAT	CGC	TCA	GCA	TAT	GTG	2740
Pro	Gly	Ala	Ala	Pro	Lys	Gln	Gly	Ala	Gly	His	Arg	Ser	Ala	Tyr	Val	
			890					895					900			
CCA	TCA	GTA	GCA	GAC	ATA	TTA	CAA	ATT	GGC	TGG	TGG	GCC	ACT	GCT	GCT	2788
Pro	Ser	Val	Ala	Asp	Ile	Leu	Gln	Ile	Gly	Trp	Trp	Ala	Thr	Ala	Ala	
		905					910					915				
GCC	TGG	TCT	ATT	CTA	CAG	CAG	TTT	CTC	TTG	AGT	TTG	ACC	TTT	CCA	CGA	2836
Ala	Trp	Ser	Ile	Leu	Gln	Gln	Phe	Leu	Leu	Ser	Leu	Thr	Phe	Pro	Arg	
	920					925					930					
CTC	CTT	GAG	GCA	GTT	GAG	ATG	GAG	GAT	GAT	GAC	TTC	ACG	GCC	TCC	CTG	2884
Leu	Leu	Glu	Ala	Val	Glu	Met	Glu	Asp	Asp	Asp	Phe	Thr	Ala	Ser	Leu	
935					940					945					950	
TCC	AAG	CAG	AGC	TGC	ATT	ACT	GAA	CAA	ACC	CAG	TAT	TTC	TTC	GAT	AAC	2932
Ser	Lys	Gln	Ser	Cys	Ile	Thr	Glu	Gln	Thr	Gln	Tyr	Phe	Phe	Asp	Asn	
				955					960					965		
GAC	AGT	AAA	TCA	TTC	AGT	GGT	GTA	TTA	GAC	TGT	GGA	AAC	TGT	TCC	AGA	2980
Asp	Ser	Lys	Ser	Phe	Ser	Gly	Val	Leu	Asp	Cys	Gly	Asn	Cys	Ser	Arg	
			970				975						980			
ATC	TTT	CAT	GGA	GAA	AAG	CTT	ATG	AAC	ACC	AAC	TTA	ATA	TTC	ATA	ATG	3028
Ile	Phe	His	Gly	Glu	Lys	Leu	Met	Asn	Thr	Asn	Leu	Ile	Phe	Ile	Met	
		985					990					995				
GTT	GAG	AGC	AAA	GGG	ACA	TGT	CCA	TGT	GAC	ACA	CGA	CTG	CTC	ATA	CAA	3076
Val	Glu	Ser	Lys	Gly	Thr	Cys	Pro	Cys	Asp	Thr	Arg	Leu	Leu	Ile	Gln	
	1000					1005					1010					
GCG	GAG	CAG	ACT	TCT	GAC	GGT	CCA	AAT	CCT	TGT	GAC	ATG	GTT	AAG	CAA	3124
Ala	Glu	Gln	Thr	Ser	Asp	Gly	Pro	Asn	Pro	Cys	Asp	Met	Val	Lys	Gln	
1015					1020					1025					1030	
CCT	AGA	TAC	CGA	AAA	GGG	CCT	GAT	GTC	TGC	TTT	GAT	AAC	AAT	GTC	TTG	3172
Pro	Arg	Tyr	Arg	Lys	Gly	Pro	Asp	Val	Cys	Phe	Asp	Asn	Asn	Val	Leu	
				1035					1040					1045		
GAG	GAT	TAT	ACT	GAC	TGT	GGT	GGT	GTT	TCT	GGA	TTA	AAT	CCC	TCC	CTG	3220

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Glu Asp Tyr Thr Asp Cys Gly Gly Val Ser Gly Leu Asn Pro Ser Leu	
1050 1055 1060	
TGG TAT ATC ATT GGA ATC CAG TTT CTA CTA CTT TGG CTG GTA TCT GGC	3268
Trp Tyr Ile Ile Gly Ile Gln Phe Leu Leu Leu Trp Leu Val Ser Gly	
1065 1070 1075	
AGC ACA CAC CGG CTG TTA TGACCTTCTA AAAACCAAAT CTGCATAGTT	3316
Ser Thr His Arg Leu Leu	
1080 108	
AAACTCCAGA CCCTGCCAAA ACATGAGCCC TGCCCTCAAT TACAGTAACG TAGGGTCAGC	3376
TATAAAATCA GACAAACATT AGCTGGGCCT GTTCCATGGC ATAACACTAA GGCGCAGACT	3436
CCTAAGGCAC CCACTGGCTG CATGTCAGGG TGTCAGATCC TTAAACGTGT GTGAATGCTG	3496
CATCATCTAT GTGTAACATC AAAGCAAAT CCTATACGTG TCCTCTATTG GAAATTTGG	3556
GCGTTTGTG TTGCATTGTT GGT	3579

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1681 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1437
- (D) OTHER INFORMATION: /standard_name= "Beta-1-1"

(ix) FEATURE:

- (A) NAME/KEY: 3'UTR
- (B) LOCATION: 1435..1681

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

ATG GTC CAG AAG ACC AGC ATG TCC CGG GGC CCT TAC CCA CCC TCC CAG	48
Met Val Gln Lys Thr Ser Met Ser Arg Gly Pro Tyr Pro Pro Ser Gln	
1 5 10 15	
GAG ATC CCC ATG GAG GTC TTC GAC CCC AGC CCG CAG GGC AAA TAC AGC	96
Glu Ile Pro Met Glu Val Phe Asp Pro Ser Pro Gln Gly Lys Tyr Ser	
20 25 30	
AAG AGG AAA GGG CGA TTC AAA CGG TCA GAT GGG AGC ACG TCC TCG GAT	144
Lys Arg Lys Gly Arg Phe Lys Arg Ser Asp Gly Ser Thr Ser Ser Asp	
35 40 45	

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ACC	ACA	TCC	AAC	AGC	TTT	GTC	CGC	CAG	GGC	TCA	GCG	GAG	TCC	TAC	ACC	192
Thr	Thr	Ser	Asn	Ser	Phe	Val	Arg	Gln	Gly	Ser	Ala	Glu	Ser	Tyr	Thr	
	50					55					60					
AGC	CGT	CCA	TCA	GAC	TCT	GAT	GTA	TCT	CTG	GAG	GAG	GAC	CGG	GAA	GCC	240
Ser	Arg	Pro	Ser	Asp	Ser	Asp	Val	Ser	Leu	Glu	Glu	Asp	Arg	Glu	Ala	
65					70					75					80	
TTA	AGG	AAG	GAA	GCA	GAG	CGC	CAG	GCA	TTA	GCG	CAG	CTC	GAG	AAG	GCC	288
Leu	Arg	Lys	Glu	Ala	Glu	Arg	Gln	Ala	Leu	Ala	Gln	Leu	Glu	Lys	Ala	
				85					90					95		
AAG	ACC	AAG	CCA	GTG	GCA	TTT	GCT	GTG	CGG	ACA	AAT	GTT	GGC	TAC	AAT	336
Lys	Thr	Lys	Pro	Val	Ala	Phe	Ala	Val	Arg	Thr	Asn	Val	Gly	Tyr	Asn	
			100					105					110			
CCG	TCT	CCA	GGG	GAT	GAG	GTG	CCT	GTG	CAG	GGA	GTG	GCC	ATC	ACC	TTC	384
Pro	Ser	Pro	Gly	Asp	Glu	Val	Pro	Val	Gln	Gly	Val	Ala	Ile	Thr	Phe	
		115					120					125				
GAG	CCC	AAA	GAC	TTC	CTG	CAC	ATC	AAG	GAG	AAA	TAC	AAT	AAT	GAC	TGG	432
Glu	Pro	Lys	Asp	Phe	Leu	His	Ile	Lys	Glu	Lys	Tyr	Asn	Asn	Asp	Trp	
130						135					140					
TGG	ATC	GGG	CGG	CTG	GTG	AAG	GAG	GGC	TGT	GAG	GTT	GGC	TTC	ATT	CCC	480
Trp	Ile	Gly	Arg	Leu	Val	Lys	Glu	Gly	Cys	Glu	Val	Gly	Phe	Ile	Pro	
145					150					155					160	
AGC	CCC	GTC	AAA	CTG	GAC	AGC	CTT	CGC	CTG	CTG	CAG	GAA	CAG	AAG	CTG	528
Ser	Pro	Val	Lys	Leu	Asp	Ser	Leu	Arg	Leu	Leu	Gln	Glu	Gln	Lys	Leu	
				165					170					175		
CGC	CAG	AAC	CGC	CTC	GGC	TCC	AGC	AAA	TCA	GGC	GAT	AAC	TCC	AGT	TCC	576
Arg	Gln	Asn	Arg	Leu	Gly	Ser	Ser	Lys	Ser	Gly	Asp	Asn	Ser	Ser	Ser	
			180					185					190			
AGT	CTG	GGA	GAT	GTG	GTG	ACT	GGC	ACC	CGC	CGC	CCC	ACA	CCC	CCT	GCC	624
Ser	Leu	Gly	Asp	Val	Val	Thr	Gly	Thr	Arg	Arg	Pro	Thr	Pro	Pro	Ala	
		195					200					205				
AGT	GGT	AAT	GAA	ATG	ACT	AAC	TTA	GCC	TTT	GAA	CTA	GAC	CCC	CTA	GAG	672
Ser	Gly	Asn	Glu	Met	Thr	Asn	Leu	Ala	Phe	Glu	Leu	Asp	Pro	Leu	Glu	
210						215					220					
TTA	GAG	GAG	GAA	GAG	GCT	GAG	CTT	GGT	GAG	CAG	AGT	GGC	TCT	GCC	AAG	720
Leu	Glu	Glu	Glu	Glu	Ala	Glu	Leu	Gly	Glu	Gln	Ser	Gly	Ser	Ala	Lys	
225					230					235					240	
ACT	AGT	GTT	AGC	AGT	GTC	ACC	ACC	CCG	CCA	CCC	CAT	GGC	AAA	CGC	ATC	768
Thr	Ser	Val	Ser	Ser	Val	Thr	Thr	Pro	Pro	Pro	His	Gly	Lys	Arg	Ile	
				245					250					255		
CCC	TTC	TTT	AAG	AAG	ACA	GAG	CAT	GTG	CCC	CCC	TAT	GAC	GTG	GTG	CCT	816
Pro	Phe	Phe	Lys	Lys	Thr	Glu	His	Val	Pro	Pro	Tyr	Asp	Val	Val	Pro	
			260					265					270			

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TCC	ATG	AGG	CCC	ATC	ATC	CTG	GTG	GGA	CCG	TCG	CTC	AAG	GGC	TAC	GAG	864
Ser	Met	Arg	Pro	Ile	Ile	Leu	Val	Gly	Pro	Ser	Leu	Lys	Gly	Tyr	Glu	
		275					280					285				
GTT	ACA	GAC	ATG	ATG	CAG	AAA	GCT	TTA	TTT	GAC	TTC	TTG	AAG	CAT	CGG	912
Val	Thr	Asp	Met	Met	Gln	Lys	Ala	Leu	Phe	Asp	Phe	Leu	Lys	His	Arg	
	290					295					300					
TTT	GAT	GGC	AGG	ATC	TCC	ATC	ACT	CGT	GTG	ACG	GCA	GAT	ATT	TCC	CTG	960
Phe	Asp	Gly	Arg	Ile	Ser	Ile	Thr	Arg	Val	Thr	Ala	Asp	Ile	Ser	Leu	
305					310					315					320	
GCT	AAG	CGC	TCA	GTT	CTC	AAC	AAC	CCC	AGC	AAA	CAC	ATC	ATC	ATT	GAG	1008
Ala	Lys	Arg	Ser	Val	Leu	Asn	Asn	Pro	Ser	Lys	His	Ile	Ile	Ile	Glu	
				325					330					335		
CGC	TCC	AAC	ACA	CGC	TCC	AGC	CTG	GCT	GAG	GTG	CAG	AGT	GAA	ATC	GAG	1056
Arg	Ser	Asn	Thr	Arg	Ser	Ser	Leu	Ala	Glu	Val	Gln	Ser	Glu	Ile	Glu	
			340					345					350			
CGA	ATC	TTC	GAG	CTG	GCC	CGG	ACC	CTT	CAG	TTG	GTC	GCT	CTG	GAT	GCT	1104
Arg	Ile	Phe	Glu	Leu	Ala	Arg	Thr	Leu	Gln	Leu	Val	Ala	Leu	Asp	Ala	
		355					360					365				
GAC	ACC	ATC	AAT	CAC	CCA	GCC	CAG	CTG	TCC	AAG	ACC	TCG	CTG	GCC	CCC	1152
Asp	Thr	Ile	Asn	His	Pro	Gln	Leu	Ser	Lys	Thr	Ser	Leu	Ala	Pro		
	370					375				380						
ATC	ATT	GTT	TAC	ATC	AAG	ATC	ACC	TCT	CCC	AAG	GTA	CTT	CAA	AGG	CTC	1200
Ile	Ile	Val	Tyr	Ile	Lys	Ile	Thr	Ser	Pro	Lys	Val	Leu	Gln	Arg	Leu	
385					390					395					400	
ATC	AAG	TCC	CGA	GGA	AAG	TCT	CAG	TCC	AAA	CAC	CTC	AAT	GTC	CAA	ATA	1248
Ile	Lys	Ser	Arg	Gly	Lys	Ser	Gln	Ser	Lys	His	Leu	Asn	Val	Gln	Ile	
				405					410					415		
GCG	GCC	TCG	GAA	AAG	CTG	GCA	CAG	TGC	CCC	CCT	GAA	ATG	TTT	GAC	ATC	1296
Ala	Ala	Ser	Glu	Lys	Leu	Ala	Gln	Cys	Pro	Pro	Glu	Met	Phe	Asp	Ile	
			420					425					430			
ATC	CTG	GAT	GAG	AAC	CAA	TTG	GAG	GAT	GCC	TGC	GAG	CAT	CTG	GCG	GAG	1344
Ile	Leu	Asp	Glu	Asn	Gln	Leu	Glu	Asp	Ala	Cys	Glu	His	Leu	Ala	Glu	
		435					440					445				
TAC	TTG	GAA	GCC	TAT	TGG	AAG	GCC	ACA	CAC	CCG	CCC	AGC	AGC	ACG	CCA	1392
Tyr	Leu	Glu	Ala	Tyr	Trp	Lys	Ala	Thr	His	Pro	Pro	Ser	Ser	Thr	Pro	
	450					455					460					
CCC	AAT	CCG	CTG	CTG	AAC	CGC	ACC	ATG	GCT	ACC	GCA	GCC	CTG	GCT		1437
Pro	Asn	Pro	Leu	Leu	Asn	Arg	Thr	Met	Ala	Thr	Ala	Ala	Leu	Ala		
465					470				475							
GCCAGCCCTG	CCCCGTGCTC	CAACCTCCAG	GTACAGGTGC	TCACCTCGCT	CAGGAGAAAC											1497
CTCGGCTTCT	GGGGCGGGCT	GGAGTCCTCA	CAGCGGGGCA	GTGTGGTGCC	CCAGGAGCAG											1557

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GAACATGCCA TGTAGTGGGC GCCCTGCCCG TCTTCCCTCC TGCTCTGGGG TCGGAACTGG 1617
 AGTGCAGGGA ACATGGAGGA GGAAGGGAAG AGCTTTATTT TGTAAAAAAA TAAGATGAGC 1677
 GGCA 1681

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1526 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..651
- (D) OTHER INFORMATION: /standard_name= "Beta-1-4"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

ATG GTC CAG AAG ACC AGC ATG TCC CGG GGC CCT TAC CCA CCC TCC CAG	48
Met Val Gln Lys Thr Ser Met Ser Arg Gly Pro Tyr Pro Pro Ser Gln	
1 5 10 15	
GAG ATC CCC ATG GAG GTC TTC GAC CCC AGC CCG CAG GGC AAA TAC AGC	96
Glu Ile Pro Met Glu Val Phe Asp Pro Ser Pro Gln Gly Lys Tyr Ser	
20 25 30	
AAG AGG AAA GGG CGA TTC AAA CGG TCA GAT GGG AGC ACG TCC TCG GAT	144
Lys Arg Lys Gly Arg Phe Lys Arg Ser Asp Gly Ser Thr Ser Ser Asp	
35 40 45	
ACC ACA TCC AAC AGC TTT GTC CGC CAG GGC TCA GCG GAG TCC TAC ACC	192
Thr Thr Ser Asn Ser Phe Val Arg Gln Gly Ser Ala Glu Ser Tyr Thr	
50 55 60	
AGC CGT CCA TCA GAC TCT GAT GTA TCT CTG GAG GAG GAC CGG GAA GCC	240
Ser Arg Pro Ser Asp Ser Asp Val Ser Leu Glu Glu Asp Arg Glu Ala	
65 70 75 80	
TTA AGG AAG GAA GCA GAG CGC CAG GCA TTA GCG CAG CTC GAG AAG GCC	288
Leu Arg Lys Glu Ala Glu Arg Gln Ala Leu Ala Gln Leu Glu Lys Ala	
85 90 95	
AAG ACC AAG CCA GTG GCA TTT GCT GTG CGG ACA AAT GTT GGC TAC AAT	336
Lys Thr Lys Pro Val Ala Phe Ala Val Arg Thr Asn Val Gly Tyr Asn	
100 105 110	
CCG TCT CCA GGG GAT GAG GTG CCT GTG CAG GGA GTG GCC ATC ACC TTC	384
Pro Ser Pro Gly Asp Glu Val Pro Val Gln Gly Val Ala Ile Thr Phe	
115 120 125	

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GAG CCC AAA GAC TTC CTG CAC ATC AAG GAG AAA TAC AAT AAT GAC TGG Glu Pro Lys Asp Phe Leu His Ile Lys Glu Lys Tyr Asn Asn Asp Trp 130 135 140	432
TGG ATC GGG CGG CTG GTG AAG GAG GGC TGT GAG GTT GGC TTC ATT CCC Trp Ile Gly Arg Leu Val Lys Glu Gly Cys Glu Val Gly Phe Ile Pro 145 150 155 160	480
AGC CCC GTC AAA CTG GAC AGC CTT CGC CTG CTG CAG GAA CAG AAG CTG Ser Pro Val Lys Leu Asp Ser Leu Arg Leu Leu Gln Glu Gln Lys Leu 165 170 175	528
CGC CAG AAC CGC CTC GGC TCC AGC AAA TCA GGC GAT AAC TCC AGT TCC Arg Gln Asn Arg Leu Gly Ser Ser Lys Ser Gly Asp Asn Ser Ser Ser 180 185 190	576
AGT CTG GGA GAT GTG GTG ACT GGC ACC CGC CGC CCC ACA CCC CCT GCC Ser Leu Gly Asp Val Val Thr Gly Thr Arg Arg Pro Thr Pro Pro Ala 195 200 205	624
AGT GAC AGA GCA TGT GCC CCC CTA TGACGTGGTG CCTTCCATGA GGCCCATCAT Ser Asp Arg Ala Cys Ala Pro Leu 210 215	678
CCTGGTGGGA CCGTCGCTCA AGGGCTACGA GGTTACAGAC ATGATGCAGA AAGCTTTATT	738
TGACTTCTTG AAGCATCGGT TTGATGGCAG GATCTCCATC ACTCGTGTGA CGGCAGATAT	798
TTCCCTGGCT AAGCGCTCAG TTCTCAACAA CCCCAGCAAA CACATCATCA TTGAGCGCTC	858
CAACACACGC TCCAGCCTGG CTGAGGTGCA GAGTGAAATC GAGCGAATCT TCGAGCTGGC	918
CCGGACCCTT CAGTTGGTCG CTCTGGATGC TGACACCATC AATCACCCAG CCCAGCTGTC	978
CAAGACCTCG CTGGCCCCCA TCATTGTTTA CATCAAGATC ACCTCTCCCA AGGTACTTCA	1038
AAGGCTCATC AAGTCCCGAG GAAAGTCTCA GTCCAAACAC CTCAATGTCC AAATAGCGGC	1098
CTCGGAAAAG CTGGCACAGT GCCCCCTGA AATGTTTGAC ATCATCCTGG ATGAGAACCA	1158
ATTGGAGGAT GCCTGCGAGC ATCTGGCGGA GACTTTGGAA GCCTATTGGA AGGCCACACA	1218
CCCGCCAGC AGCACGCCAC CCAATCCGCT GCTGAACCGC ACCATGGCTA CCGCAGCCCT	1278
GGCTGCCAGC CCTGCCCCCTG TCTCCAACCT CCAGGTACAG GTGCTCACCT CGCTCAGGAG	1338
AAACCTCGGC TTCTGGGGCG GGCTGGAGTC CTCACAGCGG GGCAGTGTGG TGCCCCAGGA	1398
GCAGGAACAT GCCATGTAGT GGGCGCCCTG CCCGTCTTCC CTCCTGCTCT GGGGTCGGAA	1458
CTGGAGTGCA GGAACATGG AGGAGGAAGG GAAGAGCTTT ATTTTGTAAG AAAATAAGAT	1518
GAGCGGCA	1526

(2) INFORMATION FOR SEQ ID NO:35:

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(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1393 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..660
- (D) OTHER INFORMATION: /standard_name= "Beta-1-5"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

ATG	GTC	CAG	AAG	ACC	AGC	ATG	TCC	CGG	GGC	CCT	TAC	CCA	CCC	TCC	CAG	48
Met	Val	Gln	Lys	Thr	Ser	Met	Ser	Arg	Gly	Pro	Tyr	Pro	Pro	Ser	Gln	
1				5					10					15		
GAG	ATC	CCC	ATG	GAG	GTC	TTC	GAC	CCC	AGC	CCG	CAG	GGC	AAA	TAC	AGC	96
Glu	Ile	Pro	Met	Glu	Val	Phe	Asp	Pro	Ser	Pro	Gln	Gly	Lys	Tyr	Ser	
			20					25					30			
AAG	AGG	AAA	GGG	CGA	TTC	AAA	CGG	TCA	GAT	GGG	AGC	ACG	TCC	TCG	GAT	144
Lys	Arg	Lys	Gly	Arg	Phe	Lys	Arg	Ser	Asp	Gly	Ser	Thr	Ser	Ser	Asp	
		35					40					45				
ACC	ACA	TCC	AAC	AGC	TTT	GTC	CGC	CAG	GGC	TCA	GCG	GAG	TCC	TAC	ACC	192
Thr	Thr	Ser	Asn	Ser	Phe	Val	Arg	Gln	Gly	Ser	Ala	Glu	Ser	Tyr	Thr	
		50				55					60					
AGC	CGT	CCA	TCA	GAC	TCT	GAT	GTA	TCT	CTG	GAG	GAG	GAC	CGG	GAA	GCC	240
Ser	Arg	Pro	Ser	Asp	Ser	Asp	Val	Ser	Leu	Glu	Glu	Asp	Arg	Glu	Ala	
65					70				75					80		
TTA	AGG	AAG	GAA	GCA	GAG	CGC	CAG	GCA	TTA	GCG	CAG	CTC	GAG	AAG	GCC	288
Leu	Arg	Lys	Glu	Ala	Glu	Arg	Gln	Ala	Leu	Ala	Gln	Leu	Glu	Lys	Ala	
			85					90						95		
AAG	ACC	AAG	CCA	GTG	GCA	TTT	GCT	GTG	CGG	ACA	AAT	GTT	GGC	TAC	AAT	336
Lys	Thr	Lys	Pro	Val	Ala	Phe	Ala	Val	Arg	Thr	Asn	Val	Gly	Tyr	Asn	
			100					105					110			
CCG	TCT	CCA	GGG	GAT	GAG	GTG	CCT	GTG	CAG	GGA	GTG	GCC	ATC	ACC	TTC	384
Pro	Ser		Gly	Asp	Glu	Val	Pro	Val	Gln	Gly	Val	Ala	Ile	Thr	Phe	
		115					120					125				
GAG	CCC	AAA	GAC	TTC	CTG	CAC	ATC	AAG	GAG	AAA	TAC	AAT	AAT	GAC	TGG	432
Glu	Pro	Lys	Asp	Phe	Leu	His	Ile	Lys	Glu	Lys	Tyr	Asn	Asn	Asp	Trp	
	130					135					140					
TGG	ATC	GGG	CGG	CTG	GTG	AAG	GAG	GGC	TGT	GAG	GTT	GGC	TTC	ATT	CCC	480
Trp	Ile	Gly	Arg	Leu	Val	Lys	Glu	Gly	Cys	Glu	Val	Gly	Phe	Ile	Pro	
145					150				155						160	

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AGC CCC GTC AAA CTG GAC AGC CTT CGC CTG CTG CAG GAA CAG AAG CTG	528
Ser Pro Val Lys Leu Asp Ser Leu Arg Leu Leu Gln Glu Gln Lys Leu	
165 170 175	
CGC CAG AAC CGC CTC GGC TCC AGC AAA TCA GGC GAT AAC TCC AGT TCC	576
Arg Gln Asn Arg Leu Gly Ser Ser Lys Ser Gly Asp Asn Ser Ser Ser	
180 185 190	
AGT CTG GGA GAT GTG GTG ACT GGC ACC CGC CGC CCC ACA CCC CCT GCC	624
Ser Leu Gly Asp Val Val Thr Gly Thr Arg Arg Pro Thr Pro Pro Ala	
195 200 205	
AGT GGT TAC AGA CAT GAT GCA GAA AGC TTT ATT TGA CTTCTTG AAGCATCGGT	677
Ser Gly Tyr Arg His Asp Ala Glu Ser Phe Ile	
210 215 220	
TTGATGGCAG GATCTCCATC ACTCGTGTGA CGGCAGATAT TTCCCTGGCT AAGCGCTCAG	737
TTCTCAACAA CCCCAGCAAA CACATCATCA TTGAGCGCTC CAACACACGC TCCAGCCTGG	797
CTGAGGTGCA GAGTGAAATC GAGCGAATCT TCGAGCTGGC CCGGACCCTT CAGTTGGTCG	857
CTCTGGATGC TGACACCATC AATCACCAG CCCAGCTGTC CAAGACCTCG CTGGCCCCCA	917
TCATTGTTTA CATCAAGATC ACCTCTCCCA AGGTACTTCA AAGGCTCATC AAGTCCCGAG	977
GAAAGTCTCA GTCCAAACAC CTCAATGTCC AAATAGCGGC CTCGGAAAAG CTGGCACAGT	1037
GGCCCCCTGA AATGTTTGAC ATCATCCTGG ATGAGAACCA ATTGGAGGAT GCCTGCGAGC	1097
ATCTGGCGGA GTACTTGGA GCCTATTGGA AGGCCACACA CCCGCCCAGC AGCACGCCAC	1157
CCAATCCGCT GCTGAACCGC ACCATGGCTA CCGCAGCCCT GGCTGCCAGC CCTGCCCCTG	1217
TCTCCAACCT CCAGGTACAG GTGCTCACCT CGCTCAGGAG AAACCTCGGC TTCTGGGGCG	1277
GGCTGGAGTC CTCACAGCGG GGCAGTGTGG TGCCCCAGGA GCAGGAACAT GCCATGTAGT	1337
GGGCGCCCTG CCCGTCTTCC CTCCTGCTCT GGGGTCGGAA CTGGAGTGCA GGGAAC	1393

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 6725 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 226..6642
- (D) OTHER INFORMATION: /standard_name= "Alpha-1C-2"

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

CTCGAGGAGG CAGTAGTGGA AAGGAGCAGT TTTTGGGGTT TGATGCCATA ATGGGAATCA	60
GGTAATCGTC GGCGGGGAAG AAGAAACGCT GCAGACCACG GCTTCCTCGA ATCTTGCGCG	120
AAAGCCGCCG GCCTCGGAGG AGGGATTAAT CCAGACCCGC CGGGGGGTGT TTTCACATTT	180
CTTCCTCTTC GTGGCTGCTC CTCCTATTAA AACCATTTTT GGTCC ATG GTC AAT	234
Met Val Asn	
1	
GAG AAT ACG AGG ATG TAC ATT CCA GAG GAA AAC CAC CAA GGT TCC AAC	282
Glu Asn Thr Arg Met Tyr Ile Pro Glu Glu Asn His Gln Gly Ser Asn	
5 10 15	
TAT GGG AGC CCA CGC CCC GCC CAT GCC AAC ATG AAT GCC AAT GCG GCA	330
Tyr Gly Ser Pro Arg Pro Ala His Ala Asn Met Asn Ala Asn Ala Ala	
20 25 30 35	
GCG GGG CTG GCC CCT GAG CAC ATC CCC ACC CCG GGG GCT GCC CTG TCG	378
Ala Gly Leu Ala Pro Glu His Ile Pro Thr Pro Gly Ala Ala Leu Ser	
40 45 50	
TGG CAG GCG GCC ATC GAC GCA GCC CGG CAG GCT AAG CTG ATG GGC AGC	426
Trp Gln Ala Ala Ile Asp Ala Ala Arg Gln Ala Lys Leu Met Gly Ser	
55 60 65	
GCT GGC AAT GCG ACC ATC TCC ACA GTC AGC TCC ACG CAG CGG AAG CGG	474
Ala Gly Asn Ala Thr Ile Ser Thr Val Ser Ser Thr Gln Arg Lys Arg	
70 75 80	
CAG CAA TAT GGG AAA CCC AAG AAG CAG GGC AGC ACC ACG GCC ACA CGC	522
Gln Gln Tyr Gly Lys Pro Lys Lys Gln Gly Ser Thr Thr Ala Thr Arg	
85 90 95	
CCG CCC CGA GCC CTG CTC TGC CTG ACC CTG AAG AAC CCC ATC CGG AGG	570
Pro Pro Arg Ala Leu Leu Cys Leu Thr Leu Lys Asn Pro Ile Arg Arg	
100 105 110 115	
GCC TGC ATC AGC ATT GTC GAA TGG AAA CCA TTT GAA ATA ATT ATT TTA	618
Ala Cys Ile Ser Ile Val Glu Trp Lys Pro Phe Glu Ile Ile Ile Leu	
120 125 130	
CTG ACT ATT TTT GCC AAT TGT GTG GCC TTA GCG ATC TAT ATT CCC TTT	666
Leu Thr Ile Phe Ala Asn Cys Val Ala Leu Ala Ile Tyr Ile Pro Phe	
135 140 145	
CCA GAA GAT GAT TCC AAC GCC ACC AAT TCC AAC CTG GAA CGA GTG GAA	714
Pro Glu Asp Asp Ser Asn Ala Thr Asn Ser Asn Leu Glu Arg Val Glu	
150 155 160	
TAT CTC TTT CTC ATA ATT TTT ACG GTG GAA GCG TTT TTA AAA GTA ATC	762
Tyr Leu Phe Leu Ile Ile Phe Thr Val Glu Ala Phe Leu Lys Val Ile	
165 170 175	

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GCC Ala 180	TAT Tyr	GGA Gly	CTC Leu	CTC Leu	TTT Phe 185	CAC His	CCC Pro	AAT Asn	GCC Ala 190	TAC Tyr	CTC Leu	CGC Arg	AAC Asn	GGC Gly	TGG Trp 195	810
AAC Asn	CTA Leu	CTA Leu	GAT Asp	TTT Phe 200	ATA Ile	ATT Ile	GTG Val	GTT Val	GTG Val 205	GGG Gly	CTT Leu	TTT Phe	AGT Ser	GCA Ala 210	ATT Ile	858
TTA Leu	GAA Glu	CAA Gln	GCA Ala 215	ACC Thr	AAA Lys	GCA Ala	GAT Asp	GGG Gly 220	GCA Ala	AAC Asn	GCT Ala	CTC Leu	GGA Gly 225	GGG Gly	AAA Lys	906
GGG Gly	GCC Ala	GGA Gly 230	TTT Phe	GAT Asp	GTG Val	AAG Lys	GCG Ala 235	CTG Leu	AGG Arg	GCC Ala	TTC Phe	CGC Arg	GTG Val	CTG Leu	CGC Arg	954
CCC Pro	CTG Leu 245	CGG Arg	CTG Leu	GTG Val	TCC Ser	GGA Gly 250	GTC Val	CCA Pro	AGT Ser	CTC Leu	CAG Gln 255	GTG Val	GTC Val	CTG Leu	AAT Asn	1002
TCC Ser 260	ATC Ile	ATC Ile	AAG Lys	GCC Ala	ATG Met 265	GTC Val	CCC Pro	CTG Leu	CTG Leu	CAC His 270	ATC Ile	GCC Ala	CTG Leu	CTT Leu	GTG Val 275	1050
CTG Leu	TTT Phe	GTC Val	ATC Ile	ATC Ile 280	ATC Ile	TAC Tyr	GCC Ala	ATC Ile	ATC Ile 285	GGC Gly	TTG Leu	GAG Glu	CTC Leu	TTC Phe 290	ATG Met	1098
GGG Gly	AAG Lys	ATG Met	CAC His 295	AAG Lys	ACC Thr	TGC Cys	TAC Tyr 300	AAC Asn	CAG Gln	GAG Glu	GGC Gly	ATA Ile 305	GCA Ala	GAT Asp	GTT Val	1146
CCA Pro	GCA Ala	GAA Glu 310	GAT Asp	GAC Asp	CCT Pro	TCC Ser	CCT Pro 315	TGT Cys	GCG Ala	CTG Leu	GAA Glu 320	ACG Thr	GGC Gly	CAC His	GGG Gly	1194
CGG Arg	CAG Gln 325	TGC Cys	CAG Gln	AAC Asn	GGC Gly	ACG Thr 330	GTG Val	TGC Cys	AAG Lys	CCC Pro	GGC Gly 335	TGG Trp	GAT Asp	GGT Gly	CCC Pro	1242
AAG Lys 340	CAC His	GGC Gly	ATC Ile	ACC Thr	AAC Asn 345	TTT Phe	GAC Asp	AAC Asn	TTT Phe 350	GCC Ala	TTC Phe	GCC Ala	ATG Met	CTC Leu	ACG Thr 355	1290
GTG Val	TTC Phe	CAG Gln	TGC Cys	ATC Ile 360	ACC Thr	ATG Met	GAG Glu	GGC Gly	TGG Trp 365	ACG Thr	GAC Asp	GTG Val	CTG Leu	TAC Tyr 370	TGG Trp	1338
GTC Val	AAT Asn	GAT Asp	GCC Ala 375	GTA Val	GGA Gly	AGG Arg	GAC Asp	TGG Trp 380	CCC Pro	TGG Trp	ATC Ile	TAT Tyr	TTT Phe 385	GTT Val	ACA Thr	1386
CTA Leu	ATC Ile	ATC Ile	ATA Ile 390	GGG Gly	TCA Ser	TTT Phe	TTT Phe 395	GTA Val	CTT Leu	AAC Asn	TTG Leu	GTT Val 400	CTC Leu	GGT Gly	GTG Val	1434

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CTT Leu	AGC Ser	GGA Gly	GAG Glu	TTT Phe	TCC Ser	AAA Lys	GAG Glu	AGG Arg	GAG Glu	AAG Lys	GCC Ala	AAG Lys	GCC Ala	CGG Arg	GGA Gly	1482
405						410					415					
GAT Asp	TTC Phe	CAG Gln	AAG Lys	CTG Leu	CGG Arg	GAG Glu	AAG Lys	CAG Gln	CAG Gln	CTA Leu	GAA Glu	GAG Glu	GAT Asp	CTC Leu	AAA Lys	1530
420					425					430					435	
GGC Gly	TAC Tyr	CTG Leu	GAT Asp	TGG Trp	ATC Ile	ACT Thr	CAG Gln	GCC Ala	GAA Glu	GAC Asp	ATC Ile	GAT Asp	CCT Pro	GAG Glu	AAT Asn	1578
				440					445					450		
GAG Glu	GAC Asp	GAA Glu	GGC Gly	ATG Met	GAT Asp	GAG Glu	GAG Glu	AAG Lys	CCC Pro	CGA Arg	AAC Asn	ATG Met	AGC Ser	ATG Met	CCC Pro	1626
			455					460					465			
ACC Thr	AGT Ser	GAG Glu	ACC Thr	GAG Glu	TCC Ser	GTC Val	AAC Asn	ACC Thr	GAA Glu	AAC Asn	GTG Val	GCT Ala	GGG Gly	GGT Gly	GAC Asp	1674
		470				475						480				
ATC Ile	GAG Glu	GGA Gly	GAA Glu	AAC Asn	TGC Cys	GGG Gly	GCC Ala	AGG Arg	CTG Leu	GCC Ala	CAC His	CGG Arg	ATC Ile	TCC Ser	AAG Lys	1722
	485					490					495					
TCA Ser	AAG Lys	TTC Phe	AGC Ser	CGC Arg	TAC Tyr	TGG Trp	CGC Arg	CGG Arg	TGG Trp	AAT Asn	CGG Arg	TTC Phe	TGC Cys	AGA Arg	AGG Arg	1770
500					505					510					515	
AAG Lys	TGC Cys	CGC Arg	GCC Ala	GCA Ala	GTC Val	AAG Lys	TCT Ser	AAT Asn	GTC Val	TTC Phe	TAC Tyr	TGG Trp	CTG Leu	GTG Val	ATT Ile	1818
				520					525					530		
TTC Phe	CTG Leu	GTG Val	TTC Phe	CTC Leu	AAC Asn	ACG Thr	CTC Leu	ACC Thr	ATT Ile	GCC Ala	TCT Ser	GAG Glu	CAC His	TAC Tyr	AAC Asn	1866
			535					540					545			
CAG Gln	CCC Pro	AAC Asn	TGG Trp	CTC Leu	ACA Thr	GAA Glu	GTC Val	CAA Gln	GAC Asp	ACG Thr	GCA Ala	AAC Asn	AAG Lys	GCC Ala	CTG Leu	1914
		550					555					560				
CTG Leu	GCC Ala	CTG Leu	TTC Phe	ACG Thr	GCA Ala	GAG Glu	ATG Met	CTC Leu	CTG Leu	AAG Lys	ATG Met	TAC Tyr	AGC Ser	CTG Leu	GGC Gly	1962
	565					570					575					
CTG Leu	CAG Gln	GCC Ala	TAC Tyr	TTC Phe	GTG Val	TCC Ser	CTC Leu	TTC Phe	AAC Asn	CGC Arg	TTT Phe	GAC Asp	TGC Cys	TTC Phe	GTC Val	2010
580					585					590					595	
GTG Val	TGT Cys	GGC Gly	GGC Gly	ATC Ile	CTG Leu	GAG Glu	ACC Thr	ATC Ile	CTG Leu	GTG Val	GAG Glu	ACC Thr	AAG Lys	ATC Ile	ATG Met	2058
				600					605					610		
TCC Ser	CCA Pro	CTG Leu	GGC Gly	ATC Ile	TCC Ser	GTG Val	CTC Leu	AGA Arg	TGC Cys	GTC Val	CGG Arg	CTG Leu	CTG Leu	AGG Arg	ATT Ile	2106
			615					620					625			

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TTC	AAG	ATC	ACG	AGG	TAC	TGG	AAC	TCC	TTG	AGC	AAC	CTG	GTG	GCA	TCC	2154
Phe	Lys	Ile	Thr	Arg	Tyr	Trp	Asn	Ser	Leu	Ser	Asn	Leu	Val	Ala	Ser	
		630					635					640				
TTG	CTG	AAC	TCT	GTG	CGC	TCC	ATC	GCC	TCC	CTG	CTC	CTT	CTC	CTC	TTC	2202
Leu	Leu	Asn	Ser	Val	Arg	Ser	Ile	Ala	Ser	Leu	Leu	Leu	Leu	Leu	Phe	
	645					650					655					
CTC	TTC	ATC	ATC	ATC	TTC	TCC	CTC	CTG	GGG	ATG	CAG	CTC	TTT	GGA	GGA	2250
Leu	Phe	Ile	Ile	Ile	Phe	Ser	Leu	Leu	Gly	Met	Gln	Leu	Phe	Gly	Gly	
660					665					670					675	
AAG	TTC	AAC	TTT	GAT	GAG	ATG	CAG	ACC	CGG	AGG	AGC	ACA	TTC	GAT	AAC	2298
Lys	Phe	Asn	Phe	Asp	Glu	Met	Gln	Thr	Arg	Arg	Ser	Thr	Phe	Asp	Asn	
				680					685					690		
TTC	CCC	CAG	TCC	CTC	CTC	ACT	GTG	TTT	CAG	ATC	CTG	ACC	GGG	GAG	GAC	2346
Phe	Pro	Gln	Ser	Leu	Leu	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gly	Glu	Asp	
			695					700					705			
TGG	AAT	TCG	GTG	ATG	TAT	GAT	GGG	ATC	ATG	GCT	TAT	GGC	GGC	CCC	TCT	2394
Trp	Asn	Ser	Val	Met	Tyr	Asp	Gly	Ile	Met	Ala	Tyr	Gly	Gly	Pro	Ser	
		710					715					720				
TTT	CCA	GGG	ATG	TTA	GTC	TGT	ATT	TAC	TTC	ATC	ATC	CTC	TTC	ATC	TGT	2442
Phe	Pro	Gly	Met	Leu	Val	Cys	Ile	Tyr	Phe	Ile	Ile	Leu	Phe	Ile	Cys	
	725					730					735					
GGA	AAC	TAT	ATC	CTA	CTG	AAT	GTG	TTC	TTG	GCC	ATT	GCT	GTG	GAC	AAC	2490
Gly	Asn	Tyr	Ile	Leu	Leu	Asn	Val	Phe	Leu	Ala	Ile	Ala	Val	Asp	Asn	
740					745					750					755	
CTG	GCT	GAT	GCT	GAG	AGC	CTC	ACA	TCT	GCC	CAA	AAG	GAG	GAG	GAA	GAG	2538
Leu	Ala	Asp	Ala	Glu	Ser	Leu	Thr	Ser	Ala	Gln	Lys	Glu	Glu	Glu	Glu	
				760					765					770		
GAG	AAG	GAG	AGA	AAG	AAG	CTG	GCC	AGG	ACT	GCC	AGC	CCA	GAG	AAG	AAA	2586
Glu	Lys	Glu	Arg	Lys	Lys	Leu	Ala	Arg	Thr	Ala	Ser	Pro	Glu	Lys	Lys	
			775					780					785			
CAA	GAG	TTG	GTG	GAG	AAG	CCG	GCA	GTG	GGG	GAA	TCC	AAG	GAG	GAG	AAG	2634
Gln	Glu	Leu	Val	Glu	Lys	Pro	Ala	Val	Gly	Glu	Ser	Lys	Glu	Glu	Lys	
		790					795					800				
ATT	GAG	CTG	AAA	TCC	ATC	ACG	GCT	GAC	GGA	GAG	TCT	CCA	CCC	GCC	ACC	2682
Ile	Glu	Leu	Lys	Ser	Ile	Thr	Ala	Asp	Gly	Glu	Ser	Pro	Pro	Ala	Thr	
	805					810					815					
AAG	ATC	AAC	ATG	GAT	GAC	CTC	CAG	CCC	AAT	GAA	AAT	GAG	GAT	AAG	AGC	2730
Lys	Ile	Asn	Met	Asp	Asp	Leu	Gln	Pro	Asn	Glu	Asn	Glu	Asp	Lys	Ser	
820					825					830					835	
CCC	TAC	CCC	AAC	CCA	GAA	ACT	ACA	GGA	GAA	GAG	GAT	GAG	GAG	GAG	CCA	2778
Pro	Tyr	Pro	Asn	Pro	Glu	Thr	Thr	Gly	Glu	Glu	Asp	Glu	Glu	Glu	Pro	
				840				845						850		

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GAG	ATG	CCT	GTC	GGC	CCT	CGC	CCA	CGA	CCA	CTC	TCT	GAG	CTT	CAC	CTT	2826
Glu	Met	Pro	Val	Gly	Pro	Arg	Pro	Arg	Pro	Leu	Ser	Glu	Leu	His	Leu	
			855					860					865			
AAG	GAA	AAG	GCA	GTG	CCC	ATG	CCA	GAA	GCC	AGC	GCG	TTT	TTC	ATC	TTC	2874
Lys	Glu	Lys	Ala	Val	Pro	Met	Pro	Glu	Ala	Ser	Ala	Phe	Phe	Ile	Phe	
		870					875					880				
AGC	TCT	AAC	AAC	AGG	TTT	CGC	CTC	CAG	TGC	CAC	CGC	ATT	GTC	AAT	GAC	2922
Ser	Ser	Asn	Asn	Arg	Phe	Arg	Leu	Gln	Cys	His	Arg	Ile	Val	Asn	Asp	
	885					890					895					
ACG	ATC	TTC	ACC	AAC	CTG	ATC	CTC	TTC	TTC	ATT	CTG	CTC	AGC	AGC	ATT	2970
Thr	Ile	Phe	Thr	Asn	Leu	Ile	Leu	Phe	Phe	Ile	Leu	Leu	Ser	Ser	Ile	
900					905					910					915	
TCC	CTG	GCT	GCT	GAG	GAC	CCG	GTC	CAG	CAC	ACC	TCC	TTC	AGG	AAC	CAT	3018
Ser	Leu	Ala	Ala	Glu	Asp	Pro	Val	Gln	His	Thr	Ser	Phe	Arg	Asn	His	
				920					925					930		
ATT	CTG	TTT	TAT	TTT	GAT	ATT	GTT	TTT	ACC	ACC	ATT	TTC	ACC	ATT	GAA	3066
Ile	Leu	Phe	Tyr	Phe	Asp	Ile	Val	Phe	Thr	Thr	Ile	Phe	Thr	Ile	Glu	
			935					940					945			
ATT	GCT	CTG	AAG	ATG	ACT	GCT	TAT	GGG	GCT	TTC	TTG	CAC	AAG	GGT	TCT	3114
Ile	Ala	Leu	Lys	Met	Thr	Ala	Tyr	Gly	Ala	Phe	Leu	His	Lys	Gly	Ser	
		950					955					960				
TTC	TGC	CGG	AAC	TAC	TTC	AAC	ATC	CTG	GAC	CTG	CTG	GTG	GTC	AGC	GTG	3162
Phe	Cys	Arg	Asn	Tyr	Phe	Asn	Ile	Leu	Asp	Leu	Leu	Val	Val	Ser	Val	
	965					970					975					
TCC	CTC	ATC	TCC	TTT	GGC	ATC	CAG	TCC	AGT	GCA	ATC	AAT	GTC	GTG	AAG	3210
Ser	Leu	Ile	Ser	Phe	Gly	Ile	Gln	Ser	Ser	Ala	Ile	Asn	Val	Val	Lys	
980					985					990					995	
ATC	TTG	CGA	GTC	CTG	CGA	GTA	CTC	AGG	CCC	CTG	AGG	GCC	ATC	AAC	AGG	3258
Ile	Leu	Arg	Val	Leu	Arg	Val	Leu	Arg	Pro	Leu	Arg	Ala	Ile	Asn	Arg	
				1000					1005					1010		
GCC	AAG	GGG	CTA	AAG	CAT	GTG	GTT	CAG	TGT	GTG	TTT	GTC	GCC	ATC	CGG	3306
Ala	Lys	Gly	Leu	Lys	His	Val	Val	Gln	Cys	Val	Phe	Val	Ala	Ile	Arg	
			1015					1020					1025			
ACC	ATC	GGG	AAC	ATC	GTG	ATT	GTC	ACC	ACC	CTG	CTG	CAG	TTC	ATG	TTT	3354
Thr	Ile	Gly	Asn	Ile	Val	Ile	Val	Thr	Thr	Leu	Leu	Gln	Phe	Met	Phe	
		1030					1035					1040				
GCC	TGC	ATC	GGG	GTC	CAG	CTC	TTC	AAG	GGA	AAG	CTG	TAC	ACC	TGT	TCA	3402
Ala	Cys	Ile	Gly	Val	Gln	Leu	Phe	Lys	Gly	Lys	Leu	Tyr	Thr	Cys	Ser	
	1045					1050					1055					
GAC	AGT	TCC	AAG	CAG	ACA	GAG	GCG	GAA	TGC	AAG	GGC	AAC	TAC	ATC	ACG	3450
Asp	Ser	Ser	Lys	Gln	Thr	Glu	Ala	Glu	Cys	Lys	Gly	Asn	Tyr	Ile	Thr	
1060					1065				1070						1075	

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TAC AAA GAC GGG GAG GTT GAC CAC CCC ATC ATC CAA CCC CGC AGC TGG	3498
Tyr Lys Asp Gly Glu Val Asp His Pro Ile Ile Gln Pro Arg Ser Trp	
1080 1085 1090	
GAG AAC AGC AAG TTT GAC TTT GAC AAT GTT CTG GCA GCC ATG ATG GCC	3546
Glu Asn Ser Lys Phe Asp Phe Asp Asn Val Leu Ala Ala Met Met Ala	
1095 1100 1105	
CTC TTC ACC GTC TCC ACC TTC GAA GGG TGG CCA GAG CTG CTG TAC CGC	3594
Leu Phe Thr Val Ser Thr Phe Glu Gly Trp Pro Glu Leu Leu Tyr Arg	
1110 1115 1120	
TCC ATC GAC TCC CAC ACG GAA GAC AAG GGC CCC ATC TAC AAC TAC CGT	3642
Ser Ile Asp Ser His Thr Glu Asp Lys Gly Pro Ile Tyr Asn Tyr Arg	
1125 1130 1135	
GTG GAG ATC TCC ATC TTC TTC ATC ATC TAC ATC ATC ATC ATC GCC TTC	3690
Val Glu Ile Ser Ile Phe Phe Ile Ile Tyr Ile Ile Ile Ile Ala Phe	
1140 1145 1150 1155	
TTC ATG ATG AAC ATC TTC GTG GGC TTC GTC ATC GTC ACC TTT CAG GAG	3738
Phe Met Met Asn Ile Phe Val Gly Phe Val Ile Val Thr Phe Gln Glu	
1160 1165 1170	
CAG GGG GAG CAG GAG TAC AAG AAC TGT GAG CTG GAC AAG AAC CAG CGA	3786
Gln Gly Glu Gln Glu Tyr Lys Asn Cys Glu Leu Asp Lys Asn Gln Arg	
1175 1180 1185	
CAG TGC GTG GAA TAC GCC CTC AAG GCC CGG CCC CTG CGG AGG TAC ATC	3834
Gln Cys Val Glu Tyr Ala Leu Lys Ala Arg Pro Leu Arg Arg Tyr Ile	
1190 1195 1200	
CCC AAG AAC CAG CAC CAG TAC AAA GTG TGG TAC GTG GTC AAC TCC ACC	3882
Pro Lys Asn Gln His Gln Tyr Lys Val Trp Tyr Val Val Asn Ser Thr	
1205 1210 1215	
TAC TTC GAG TAC CTG ATG TTC GTC CTC ATC CTG CTC AAC ACC ATC TGC	3930
Tyr Phe Glu Tyr Leu Met Phe Val Leu Ile Leu Leu Asn Thr Ile Cys	
1220 1225 1230 1235	
CTG GCC ATG CAG CAC TAC GGC CAG AGC TGC CTG TTC AAA ATC GCC ATG	3978
Leu Ala Met Gln His Tyr Gly Gln Ser Cys Leu Phe Lys Ile Ala Met	
1240 1245 1250	
AAC ATC CTC AAC ATG CTC TTC ACT GGC CTC TTT ACC GTG GAG ATG ATC	4026
Asn Ile Leu Asn Met Leu Phe Thr Gly Leu Phe Thr Val Glu Met Ile	
1255 1260 1265	
CTG AAG CTC ATT GCC TTC AAA CCC AAG CAC TAT TTC TGT GAT GCA TGG	4074
Leu Lys Leu Ile Ala Phe Lys Pro Lys His Tyr Phe Cys Asp Ala Trp	
1270 1275 1280	
AAT ACA TTT GAC GCC TTG ATT GTT GTG GGT AGC ATT GTT GAT ATA GCA	4122
Asn Thr Phe Asp Ala Leu Ile Val Val Gly Ser Ile Val Asp Ile Ala	
1285 1290 1295	

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ATC ACC GAG GTA AAC CCA GCT GAA CAT ACC CAA TGC TCT CCC TCT ATG Ile Thr Glu Val Asn Pro Ala Glu His Thr Gln Cys Ser Pro Ser Met 1300 1305 1310 1315	4170
AAC GCA GAG GAA AAC TCC CGC ATC TCC ATC ACC TTC TTC CGC CTG TTC Asn Ala Glu Glu Asn Ser Arg Ile Ser Ile Thr Phe Phe Arg Leu Phe 1320 1325 1330	4218
CGG GTC ATG CGT CTG GTG AAG CTG CTG AGC CGT GGG GAG GGC ATC CGG Arg Val Met Arg Leu Val Lys Leu Leu Ser Arg Gly Glu Gly Ile Arg 1335 1340 1345	4266
ACG CTG CTG TGG ACC TTC ATC AAG TCC TTC CAG GCC CTG CCC TAT GTG Thr Leu Leu Trp Thr Phe Ile Lys Ser Phe Gln Ala Leu Pro Tyr Val 1350 1355 1360	4314
GCC CTC CTG ATC GTG ATG CTG TTC TTC ATC TAC GCG GTG ATC GGG ATG Ala Leu Leu Ile Val Met Leu Phe Phe Ile Tyr Ala Val Ile Gly Met 1365 1370 1375	4362
CAG GTG TTT GGG AAA ATT GCC CTG AAT GAT ACC ACA GAG ATC AAC CGG Gln Val Phe Gly Lys Ile Ala Leu Asn Asp Thr Thr Glu Ile Asn Arg 1380 1385 1390 1395	4410
AAC AAC AAC TTT CAG ACC TTC CCC CAG GCC GTG CTG CTC CTC TTC AGG Asn Asn Asn Phe Gln Thr Phe Pro Gln Ala Val Leu Leu Leu Phe Arg 1400 1405 1410	4458
TGT GCC ACC GGG GAG GCC TGG CAG GAC ATC ATG CTG GCC TGC ATG CCA Cys Ala Thr Gly Glu Ala Trp Gln Asp Ile Met Leu Ala Cys Met Pro 1415 1420 1425	4506
GGC AAG AAG TGT GCC CCA GAG TCC GAG CCC AGC AAC AGC ACG GAG GGT Gly Lys Lys Cys Ala Pro Glu Ser Glu Pro Ser Asn Ser Thr Glu Gly 1430 1435 1440	4554
GAA ACA CCC TGT GGT AGC AGC TTT GCT GTC TTC TAC TTC ATC AGC TTC Glu Thr Pro Cys Gly Ser Ser Phe Ala Val Phe Tyr Phe Ile Ser Phe 1445 1450 1455	4602
TAC ATG CTC TGT GCC TTC CTG ATC ATC AAC CTC TTT GTA GCT GTC ATC Tyr Met Leu Cys Ala Phe Leu Ile Ile Asn Leu Phe Val Ala Val Ile 1460 1465 1470 1475	4650
ATG GAC AAC TTT GAC TAC CTG ACA AGG GAC TGG TCC ATC CTT GGT CCC Met Asp Asn Phe Asp Tyr Leu Thr Arg Asp Trp Ser Ile Leu Gly Pro 1480 1485 1490	4698
CAC CAC CTG GAT GAG TTT AAA AGA ATC TGG GCA GAG TAT GAC CCT GAA His His Leu Asp Glu Phe Lys Arg Ile Trp Ala Glu Tyr Asp Pro Glu 1495 1500 1505	4746
GCC AAG GGT CGT ATC AAA CAC CTG GAT GTG GTG ACC CTC CTC CGG CGG Ala Lys Gly Arg Ile Lys His Leu Asp Val Val Thr Leu Leu Arg Arg 1510 1515 1520	4794

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ATT CAG CCG CCA CTA GGT TTT GGG AAG CTG TGC CCT CAC CGC GTG GCT Ile Gln Pro Pro Leu Gly Phe Gly Lys Leu Cys Pro His Arg Val Ala 1525 1530 1535	4842
TGC AAA CGC CTG GTC TCC ATG AAC ATG CCT CTG AAC AGC GAC GGG ACA Cys Lys Arg Leu Val Ser Met Asn Met Pro Leu Asn Ser Asp Gly Thr 1540 1545 1550 1555	4890
GTC ATG TTC AAT GCC ACC CTG TTT GCC CTG GTC AGG ACG GCC CTG AGG Val Met Phe Asn Ala Thr Leu Phe Ala Leu Val Arg Thr Ala Leu Arg 1560 1565 1570	4938
ATC AAA ACA GAA GGG AAC CTA GAA CAA GCC AAT GAG GAG CTG CGG GCG Ile Lys Thr Glu Gly Asn Leu Glu Gln Ala Asn Glu Glu Leu Arg Ala 1575 1580 1585	4986
ATC ATC AAG AAG ATC TGG AAG CGG ACC AGC ATG AAG CTG CTG GAC CAG Ile Ile Lys Lys Ile Trp Lys Arg Thr Ser Met Lys Leu Leu Asp Gln 1590 1595 1600	5034
GTG GTG CCC CCT GCA GGT GAT GAT GAG GTC ACC GTT GGC AAG TTC TAC Val Val Pro Pro Ala Gly Asp Asp Glu Val Thr Val Gly Lys Phe Tyr 1605 1610 1615	5082
GCC ACG TTC CTG ATC CAG GAG TAC TTC CGG AAG TTC AAG AAG CGC AAA Ala Thr Phe Leu Ile Gln Glu Tyr Phe Arg Lys Phe Lys Lys Arg Lys 1620 1625 1630 1635	5130
GAG CAG GGC CTT GTG GGC AAG CCC TCC CAG AGG AAC GCG CTG TCT CTG Glu Gln Gly Leu Val Gly Lys Pro Ser Gln Arg Asn Ala Leu Ser Leu 1640 1645 1650	5178
CAG GCT GGC TTG CGC ACA CTG CAT GAC ATC GGG CCT GAG ATC CGA CGG Gln Ala Gly Leu Arg Thr Leu His Asp Ile Gly Pro Glu Ile Arg Arg 1655 1660 1665	5226
GCC ATC TCT GGA GAT CTC ACC GCT GAG GAG GAG CTG GAC AAG GCC ATG Ala Ile Ser Gly Asp Leu Thr Ala Glu Glu Glu Leu Asp Lys Ala Met 1670 1675 1680	5274
AAG GAG GCT GTG TCC GCT GCT TCT GAA GAT GAC ATC TTC AGG AGG GCC Lys Glu Ala Val Ser Ala Ala Ser Glu Asp Asp Ile Phe Arg Arg Ala 1685 1690 1695	5322
GGT GGC CTG TTC GGC AAC CAC GTC AGC TAC TAC CAA AGC GAC GGC CGG Gly Gly Leu Phe Gly Asn His Val Ser Tyr Tyr Gln Ser Asp Gly Arg 1700 1705 1710 1715	5370
AGC GCC TTC CCC CAG ACC TTC ACC ACT CAG CGC CCG CTG CAC ATC AAC Ser Ala Phe Pro Gln Thr Phe Thr Thr Gln Arg Pro Leu His Ile Asn 1720 1725 1730	5418
AAG GCG GGC AGC AGC CAG GGC GAC ACT GAG TCG CCA TCC CAC GAG AAG Lys Ala Gly Ser Ser Gln Gly Asp Thr Glu Ser Pro Ser His Glu Lys 1735 1740 1745	5466

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CTG	GTG	GAC	TCC	ACC	TTC	ACC	CCG	AGC	AGC	TAC	TCG	TCC	ACC	GGC	TCC	5514
Leu	Val	Asp	Ser	Thr	Phe	Thr	Pro	Ser	Ser	Tyr	Ser	Ser	Thr	Gly	Ser	
		1750					1755					1760				
AAC	GCC	AAC	ATC	AAC	AAC	GCC	AAC	AAC	ACC	GCC	CTG	GGT	CGC	CTC	CCT	5562
Asn	Ala	Asn	Ile	Asn	Asn	Ala	Asn	Asn	Thr	Ala	Leu	Gly	Arg	Leu	Pro	
	1765					1770					1775					
CGC	CCC	GCC	GGC	TAC	CCC	AGC	ACG	GTC	AGC	ACT	GTG	GAG	GGC	CAC	GGG	5610
Arg	Pro	Ala	Gly	Tyr	Pro	Ser	Thr	Val	Ser	Thr	Val	Glu	Gly	His	Gly	
1780					1785					1790					1795	
CCC	CCC	TTG	TCC	CCT	GCC	ATC	CGG	GTG	CAG	GAG	GTG	GCG	TGG	AAG	CTC	5658
Pro	Pro	Leu	Ser	Pro	Ala	Ile	Arg	Val	Gln	Glu	Val	Ala	Trp	Lys	Leu	
				1800					1805					1810		
AGC	TCC	AAC	AGG	TGC	CAC	TCC	CGG	GAG	AGC	CAG	GCA	GCC	ATG	GCG	GGT	5706
Ser	Ser	Asn	Arg	Cys	His	Ser	Arg	Glu	Ser	Gln	Ala	Ala	Met	Ala	Gly	
		1815						1820					1825			
CAG	GAG	GAG	ACG	TCT	CAG	GAT	GAG	ACC	TAT	GAA	GTG	AAG	ATG	AAC	CAT	5754
Gln	Glu	Glu	Thr	Ser	Gln	Asp	Glu	Thr	Tyr	Glu	Val	Lys	Met	Asn	His	
		1830					1835					1840				
GAC	ACG	GAG	GCC	TGC	AGT	GAG	CCC	AGC	CTG	CTC	TCC	ACA	GAG	ATG	CTC	5802
Asp	Thr	Glu	Ala	Cys	Ser	Glu	Pro	Ser	Leu	Leu	Ser	Thr	Glu	Met	Leu	
	1845					1850					1855					
TCC	TAC	CAG	GAT	GAC	GAA	AAT	CGG	CAA	CTG	ACG	CTC	CCA	GAG	GAG	GAC	5850
Ser	Tyr	Gln	Asp	Asp	Glu	Asn	Arg	Gln	Leu	Thr	Leu	Pro	Glu	Glu	Asp	
1860					1865				1870						1875	
AAG	AGG	GAC	ATC	CGG	CAA	TCT	CCG	AAG	AGG	GGT	TTC	CTC	CGC	TCT	GCC	5898
Lys	Arg	Asp	Ile	Arg	Gln	Ser	Pro	Lys	Arg	Gly	Phe	Leu	Arg	Ser	Ala	
			1880					1885						1890		
TCA	CTA	GGT	CGA	AGG	GCC	TCC	TTC	CAC	CTG	GAA	TGT	CTG	AAG	CGA	CAG	5946
Ser	Leu	Gly	Arg	Arg	Ala	Ser	Phe	His	Leu	Glu	Cys	Leu	Lys	Arg	Gln	
			1895					1900					1905			
AAG	GAC	CGA	GGG	GGA	GAC	ATC	TCT	CAG	AAG	ACA	GTC	CTG	CCC	TTG	CAT	5994
Lys	Asp	Arg	Gly	Gly	Asp	Ile	Ser	Gln	Lys	Thr	Val	Leu	Pro	Leu	His	
	1910						1915					1920				
CTG	GTT	CAT	CAT	CAG	GCA	TTG	GCA	GTG	GCA	GGC	CTG	AGC	CCC	CTC	CTC	6042
Leu	Val	His	His	Gln	Ala	Leu	Ala	Val	Ala	Gly	Leu	Ser	Pro	Leu	Leu	
	1925					1930					1935					
CAG	AGA	AGC	CAT	TCC	CCT	GCC	TCA	TTC	CCT	AGG	CCT	TTT	GCC	ACC	CCA	6090
Gln	Arg	Ser	His	Ser	Pro	Ala	Ser	Phe	Pro	Arg	Pro	Phe	Ala	Thr	Pro	
1940					1945					1950					1955	
CCA	GCC	ACA	CCT	GGC	AGC	CGA	GGC	TGG	CCC	CCA	CAG	CCC	GTC	CCC	ACC	6138
Pro	Ala	Thr	Pro	Gly	Ser	Arg	Gly	Trp	Pro	Pro	Gln	Pro	Val	Pro	Thr	
				1960					1965					1970		

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CTG CGG CTT GAG GGG GTC GAG TCC AGT GAG AAA CTC AAC AGC AGC TTC Leu Arg Leu Glu Gly Val Glu Ser Ser Glu Lys Leu Asn Ser Ser Phe 1975 1980 1985	6186
CCA TCC ATC CAC TGC GGC TCC TGG GCT GAG ACC ACC CCC GGT GGC GGG Pro Ser Ile His Cys Gly Ser Trp Ala Glu Thr Thr Pro Gly Gly Gly 1990 1995 2000	6234
GGC AGC AGC GCC GCC CGG AGA GTC CGG CCC GTC TCC CTC ATG GTG CCC Gly Ser Ser Ala Ala Arg Arg Val Arg Pro Val Ser Leu Met Val Pro 2005 2010 2015	6282
AGC CAG GCT GGG GCC CCA GGG AGG CAG TTC CAC GGC AGT GCC AGC AGC Ser Gln Ala Gly Ala Pro Gly Arg Gln Phe His Gly Ser Ala Ser Ser 2020 2025 2030 2035	6330
CTG GTG GAA GCG GTC TTG ATT TCA GAA GGA CTG GGG CAG TTT GCT CAA Leu Val Glu Ala Val Leu Ile Ser Glu Gly Leu Gly Gln Phe Ala Gln 2040 2045 2050	6378
GAT CCC AAG TTC ATC GAG GTC ACC ACC CAG GAG CTG GCC GAC GCC TGC Asp Pro Lys Phe Ile Glu Val Thr Thr Gln Glu Leu Ala Asp Ala Cys 2055 2060 2065	6426
GAC ATG ACC ATA GAG GAG ATG GAG AGC GCG GCC GAC AAC ATC CTC AGC Asp Met Thr Ile Glu Glu Met Glu Ser Ala Ala Asp Asn Ile Leu Ser 2070 2075 2080	6474
GGG GGC GCC CCA CAG AGC CCC AAT GGC GCC CTC TTA CCC TTT GTG AAC Gly Gly Ala Pro Gln Ser Pro Asn Gly Ala Leu Leu Pro Phe Val Asn 2085 2090 2095	6522
TGC AGG GAC GCG GGG CAG GAC CGA GCC GGG GGC GAA GAG GAC GCG GGC Cys Arg Asp Ala Gly Gln Asp Arg Ala Gly Gly Glu Glu Asp Ala Gly 2100 2105 2110 2115	6570
TGT GTG CGC GCG CGG GGT CGA CCG AGT GAG GAG GAG CTC CAG GAC AGC Cys Val Arg Ala Arg Gly Arg Pro Ser Glu Glu Glu Leu Gln Asp Ser 2120 2125 2130	6618
AGG GTC TAC GTC AGC AGC CTG TAGTGGGCGC TGCCAGATGC GGGCTTTTTT Arg Val Tyr Val Ser Ser Leu 2135	6669
TTATTTGTTT CAATGTTTCCT AATGGGTTTCG TTTCAGAAGT GCCTCACTGT TCTCGT	6725

(2) INFORMATION FOR SEQ ID NO:37:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 2970 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

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(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 502..2316

(D) OTHER INFORMATION: /standard_name= "Beta-2C"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

CAGCAGCGTG CTAAGAAGCA GTCACATAAA CAGCAGCAGG AGTAGGCCTC CTGCTTTTCA	60
AAAGCAGAGT ACTGCAGGGT CGCGAAATGC AAGACACTCA GATGTTTGAA AATCTCCCGA	120
GTTGAGAATG GCTACTGTAA AAGCGTCACC AAGAACTCT GACGATCTGG ACAGTCCTAA	180
CTCTGTGTGA GCAATACTTA CTTCCGGAAA ATTAATGCTA CTTCTTGTAG ATTTTGTCAA	240
ATAGGAAACC CCCTTGAAGA AGATCTCAAA TTACGCCCCC CACCCCCAAA AAAAGACAAA	300
CAGGGGAGAA CAAAGTTTTG GCATGCCTGC AGGAACGGTG GCTTTTTTTAG AAACCTACCTA	360
GGAGGCAGAA GCTAAGTGAT TTGCTCATGC CTCTTACCTG GGAGTAGAAG GTGGGAAGAA	420
ATGGACCGAG GCTGTGACGA GAAGACAAGG CACAGTGCAG CTTGGTGAAG CCACACGCTG	480
ACTGCGTTCT GCCCCTCTT C ATG CAG TGC TGC GGG CTG GTG CAT CGC CGG	531
Met Gln Cys Cys Gly Leu Val His Arg Arg	
1 5 10	
CGA GTA CGG GTG TCC TAT GGT TCG GCA GAC TCC TAC ACT AGC CGT CCA	579
Arg Val Arg Val Ser Tyr Gly Ser Ala Asp Ser Tyr Thr Ser Arg Pro	
15 20 25	
TCC GAT TCC GAT GTA TCT CTG GAG GAG GAC CGG GAG GCA GTG CGC AGA	627
Ser Asp Ser Asp Val Ser Leu Glu Glu Asp Arg Glu Ala Val Arg Arg	
30 35 40	
GAA GCG GAG CGG CAG GCC CAG GCA CAG TTG GAA AAA GCA AAG ACA AAG	675
Glu Ala Glu Arg Gln Ala Gln Ala Gln Leu Glu Lys Ala Lys Thr Lys	
45 50 55	
CCC GTT GCA TTT GCG GTT CGG ACA AAT GTC AGC TAC AGT GCG GCC CAT	723
Pro Val Ala Phe Ala Val Arg Thr Asn Val Ser Tyr Ser Ala Ala His	
60 65 70	
GAA GAT GAT GTT CCA GTG CCT GGC ATG GCC ATC TCA TTC GAA GCA AAA	771
Glu Asp Asp Val Pro Val Pro Gly Met Ala Ile Ser Phe Glu Ala Lys	
75 80 85 90	
GAT TTT CTG CAT GTT AAG GAA AAA TTT AAC AAT GAC TGG TGG ATA GGG	819
Asp Phe Leu His Val Lys Glu Lys Phe Asn Asn Asp Trp Trp Ile Gly	
95 100 105	
CGA TTG GTA AAA GAA GGC TGT GAA ATC GGA TTC ATT CCA AGC CCA GTC	867
Arg Leu Val Lys Glu Gly Cys Glu Ile Gly Phe Ile Pro Ser Pro Val	
110 115 120	

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AAA CTA GAA AAC ATG AGG CTG CAG CAT GAA CAG AGA GCC AAG CAA GGG Lys Leu Glu Asn Met Arg Leu Gln His Glu Gln Arg Ala Lys Gln Gly 125 130 135	915
AAA TTC TAC TCC AGT AAA TCA GGA GGA AAT TCA TCA TCC AGT TTG GGT Lys Phe Tyr Ser Ser Lys Ser Gly Gly Asn Ser Ser Ser Ser Leu Gly 140 145 150	963
GAC ATA GTA CCT AGT TCC AGA AAA TCA ACA CCT CCA TCA TCT GCT ATA Asp Ile Val Pro Ser Ser Arg Lys Ser Thr Pro Pro Ser Ser Ala Ile 155 160 165 170	1011
GAC ATA GAT GCT ACT GGC TTA GAT GCA GAA GAA AAT GAT ATT CCA GCA Asp Ile Asp Ala Thr Gly Leu Asp Ala Glu Glu Asn Asp Ile Pro Ala 175 180 185	1059
AAC CAC CGC TCC CCT AAA CCC AGT GCA AAC AGT GTA ACG TCA CCC CAC Asn His Arg Ser Pro Lys Pro Ser Ala Asn Ser Val Thr Ser Pro His 190 195 200	1107
TCC AAA GAG AAA AGA ATG CCC TTC TTT AAG AAG ACA GAG CAC ACT CCT Ser Lys Glu Lys Arg Met Pro Phe Phe Lys Lys Thr Glu His Thr Pro 205 210 215	1155
CCG TAT GAT GTG GTA CCT TCC ATG CGA CCA GTG GTC CTA GTG GGC CCT Pro Tyr Asp Val Val Pro Ser Met Arg Pro Val Val Leu Val Gly Pro 220 225 230	1203
TCT CTG AAG GGC TAC GAG GTC ACA GAT ATG ATG CAA AAA GCG CTG TTT Ser Leu Lys Gly Tyr Glu Val Thr Asp Met Met Gln Lys Ala Leu Phe 235 240 245 250	1251
GAT TTT TTA AAA CAC AGA TTT GAA GGG CGG ATA TCC ATC ACA AGG GTC Asp Phe Leu Lys His Arg Phe Glu Gly Arg Ile Ser Ile Thr Arg Val 255 260 265	1299
ACC GCT GAC ATC TCG CTT GCC AAA CGC TCG GTA TTA AAC AAT CCC AGT Thr Ala Asp Ile Ser Leu Ala Lys Arg Ser Val Leu Asn Asn Pro Ser 270 275 280	1347
AAG CAC GCA ATA ATA GAA AGA TCC AAC ACA AGG TCA AGC TTA GCG GAA Lys His Ala Ile Ile Glu Arg Ser Asn Thr Arg Ser Ser Leu Ala Glu 285 290 295	1395
GTT CAG AGT GAA ATC GAA AGG ATT TTT GAA CTT GCA AGA ACA TTG CAG Val Gln Ser Glu Ile Glu Arg Ile Phe Glu Leu Ala Arg Thr Leu Gln 300 305 310	1443
TTG GTG GTC CTT GAC GCG GAT ACA ATT AAT CAT CCA GCT CAA CTC AGT Leu Val Val Leu Asp Ala Asp Thr Ile Asn His Pro Ala Gln Leu Ser 315 320 325 330	1491
AAA ACC TCC TTG GCC CCT ATT ATA GTA TAT GTA AAG ATT TCT TCT CCT Lys Thr Ser Leu Ala Pro Ile Ile Val Tyr Val Lys Ile Ser Ser Pro 335 340 345	1539

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AAG Lys	GTT Val	TTA Leu	CAA Gln 350	AGG Arg	TTA Leu	ATA Ile	AAA Lys	TCT Ser 355	CGA Arg	GGG Gly	AAA Lys	TCT Ser	CAA Gln 360	GCT Ala	AAA Lys	1587
CAC His	CTC Leu	AAC Asn 365	GTC Val	CAG Gln	ATG Met	GTA Val	GCA Ala 370	GCT Ala	GAT Asp	AAA Lys	CTG Leu 375	GCT Ala	CAG Gln	TGT Cys	CCT Pro	1635
CCA Pro	GAG Glu 380	CTG Leu	TTC Phe	GAT Asp	GTG Val	ATC Ile 385	TTG Leu	GAT Asp	GAG Glu	AAC Asn 390	CAG Gln	CTT Leu	GAG Glu	GAT Asp	GCC Ala	1683
TGT Cys 395	GAG Glu	CAC His	CTT Leu	GCC Ala	GAC Asp 400	TAT Tyr	CTG Leu	GAG Glu	GCC Ala	TAC Tyr 405	TGG Trp	AAG Lys	GCC Ala	ACC Thr	CAT His 410	1731
CCT Pro	CCC Pro	AGC Ser	AGT Ser	AGC Ser 415	CTC Leu	CCC Pro	AAC Asn	CCT Pro	CTC Leu 420	CTT Leu	AGC Ser	CGT Arg	ACA Thr	TTA Leu 425	GCC Ala	1779
ACT Thr	TCA Ser	AGT Ser	CTG Leu 430	CCT Pro	CTT Leu	AGC Ser	CCC Pro	ACC Thr 435	CTA Leu	GCC Ala	TCT Ser	AAT Asn 440	TCA Ser	CAG Gln	GGT Gly	1827
TCT Ser	CAA Gln 445	GGT Gly	GAT Asp	CAG Gln	AGG Arg	ACT Thr	GAT Asp 450	CGC Arg	TCC Ser	GCT Ala	CCT Pro	ATC Ile 455	CGT Arg	TCT Ser	GCT Ala	1875
TCC Ser 460	CAA Gln 460	GCT Ala	GAA Glu	GAA Glu	GAA Glu	CCT Pro 465	AGT Ser	GTG Val	GAA Glu	CCA Pro	GTC Val 470	AAG Lys	AAA Lys	TCC Ser	CAG Gln	1923
CAC His 475	CGC Arg	TCT Ser	TCC Ser	TCC Ser	TCA Ser 480	GCC Ala	CCA Pro	CAC His	CAC His	AAC Asn 485	CAT His	CGC Arg	AGT Ser	GGG Gly	ACA Thr 490	1971
AGT Ser	CGC Arg	GGC Gly	CTC Leu	TCC Ser 495	AGG Arg	CAA Gln	GAG Glu	ACA Thr 500	TTT Phe	GAC Asp	TCG Ser	GAA Glu	ACC Thr	CAG Gln 505	GAG Glu	2019
AGT Ser	CGA Arg	GAC Asp	TCT Ser 510	GCC Ala	TAC Tyr	GTA Val	GAG Glu	CCA Pro 515	AAG Lys	GAA Glu	GAT Asp	TAT Tyr	TCC Ser 520	CAT His	GAC Asp	2067
CAC His	GTG Val 525	GAC Asp	CAC His	TAT Tyr	GCC Ala	TCA Ser	CAC His 530	CGT Arg	GAC Asp	CAC His	AAC Asn 535	CAC His	AGA Arg	GAC Asp	GAG Glu	2115
ACC Thr	CAC His 540	GGG Gly	AGC Ser	AGT Ser	GAC Asp	CAC His 545	AGA Arg	CAC His	AGG Arg	GAG Glu	TCC Ser 550	CGG Arg	CAC His	CGT Arg	TCC Ser	2163
CGG Arg 555	GAC Asp	GTG Val	GAT Asp	CGA Arg	GAG Glu	CAG Gln 560	GAC Asp	CAC His	AAC Asn	GAG Glu 565	TGC Cys	AAC Asn	AAG Lys	CAG Gln	CGC Arg 570	2211

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AGC CGT CAT AAA TCC AAG GAT CGC TAC TGT GAA AAG GAT GGA GAA GTG	2259
Ser Arg His Lys Ser Lys Asp Arg Tyr Cys Glu Lys Asp Gly Glu Val	
575 580 585	
ATA TCA AAA AAA CGG AAT GAG GCT GGG GAG TGG AAC AGG GAT GTT TAC	2307
Ile Ser Lys Lys Arg Asn Glu Ala Gly Glu Trp Asn Arg Asp Val Tyr	
590 595 600	
ATC CCC CAA TGAGTTTGC CCTTTTGTGT TTTTTTTTTT TTTTTTTTGA	2356
Ile Pro Gln	
605	
AGTCTTGTAT AACTAACAGC ATCCCCAAAA CAAAAAGTCT TTGGGGTCTA CACTGCAATC	2416
ATATGTGATC TGTCTTGTA TATTTTGTAT TATTGCTGTT GCTTGAATAG CAATAGCATG	2476
GATAGAGTAT TGAGATACTT TTTCTTTTGT AAGTGCTACA TAAATTGGCC TGGTATGGCT	2536
GCAGTCCTCC GGTTCATAC TGGACTCTTC AAAAAGTGT TTGGGTAGCT GCCACTTGAA	2596
CAAAATCTGT TGCCACCCAG GTGATGTTAG TGTTTTAAGA AATGTAGTTG ATGTATCCAA	2656
CAAGCCAGAA TCAGCACAGA TAAAAAGTGG AATTTCTTGT TTCTCCAGAT TTTTAATACG	2716
TTAATACGCA GGCATCTGAT TTGCATATTC ATTCATGGAC CACTGTTTCT TGCTTGTACC	2776
TCTGGCTGAC TAAATTTGGG GACAGATTCA GTCTTGCTT ACACAAAGGG GATCATAAAG	2836
TTAGAATCTA TTTTCTATGT ACTAGTACTG TGTACTGTAT AGACAGTTTG TAAATGTTAT	2896
TTCTGCAAAC AAACACCTCC TTATTATATA TAATATATAT ATATATATCA GTTTGATCAC	2956
ACTATTTTAG AGTC	2970

(2) INFORMATION FOR SEQ ID NO:38:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2712 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 - (A) NAME/KEY: CDS
 - (B) LOCATION: 223..2061
 - (D) OTHER INFORMATION: /standard_name= "Beta-2E"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

AGTGTGTGTT TTCAGCCCCT CCTGGAATGG GAAAATAAGA ATCTCCCTGG ATGGGAGTCC	60
TCTGGGGCAG GGAGTGAAAG CCCCAGGAGGC AGAAAGGGAC GGAGAACAGG GGCTTGCCCA	120

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GAGCATGGAT AGGAAAGGAG CTGGGGTTCT CCGGGGCTCA GCGCGCACTG AGAACCTGTG	180
CCCCGGGGCTG CAGCTGCGGA CGATAAAGGC GCTGTCTGGC TC ATG AAG GCC ACC	234
Met Lys Ala Thr	
1	
TGG ATC AGG CTT CTG AAA AGA GCC AAG GGA GGA AGG CTG AAG AAT TCT	282
Trp Ile Arg Leu Leu Lys Arg Ala Lys Gly Gly Arg Leu Lys Asn Ser	
5 10 15 20	
GAT ATC TGT GGT TCG GCA GAC TCC TAC ACT AGC CGT CCA TCC GAT TCC	330
Asp Ile Cys Gly Ser Ala Asp Ser Tyr Thr Ser Arg Pro Ser Asp Ser	
25 30 35	
GAT GTA TCT CTG GAG GAG GAC CGG GAG GCA GTG CGC AGA GAA GCG GAG	378
Asp Val Ser Leu Glu Glu Asp Arg Glu Ala Val Arg Arg Glu Ala Glu	
40 45 50	
CGG CAG GCC CAG GCA CAG TTG GAA AAA GCA AAG ACA AAG CCC GTT GCA	426
Arg Gln Ala Gln Ala Gln Leu Glu Lys Ala Lys Thr Lys Pro Val Ala	
55 60 65	
TTT GCG GTT CGG ACA AAT GTC AGC TAC AGT GCG GCC CAT GAA GAT GAT	474
Phe Ala Val Arg Thr Asn Val Ser Tyr Ser Ala Ala His Glu Asp Asp	
70 75 80	
GTT CCA GTG CCT GGC ATG GCC ATC TCA TTC GAA GCA AAA GAT TTT CTG	522
Val Pro Val Pro Gly Met Ala Ile Ser Phe Glu Ala Lys Asp Phe Leu	
85 90 95 100	
CAT GTT AAG GAA AAA TTT AAC AAT GAC TGG TGG ATA GGG CGA TTG GTA	570
His Val Lys Glu Lys Phe Asn Asn Asp Trp Trp Ile Gly Arg Leu Val	
105 110 115	
AAA GAA GGC TGT GAA ATC GGA TTC ATT CCA AGC CCA GTC AAA CTA GAA	618
Lys Glu Gly Cys Glu Ile Gly Phe Ile Pro Ser Pro Val Lys Leu Glu	
120 125 130	
AAC ATG AGG CTG CAG CAT GAA CAG AGA GCC AAG CAA GGG AAA TTC TAC	666
Asn Met Arg Leu Gln His Glu Gln Arg Ala Lys Gln Gly Lys Phe Tyr	
135 140 145	
TCC AGT AAA TCA GGA GGA AAT TCA TCA TCC AGT TTG GGT GAC ATA GTA	714
Ser Ser Lys Ser Gly Gly Asn Ser Ser Ser Ser Leu Gly Asp Ile Val	
150 155 160	
CCT AGT TCC AGA AAA TCA ACA CCT CCA TCA TCT GCT ATA GAC ATA GAT	762
Pro Ser Ser Arg Lys Ser Thr Pro Pro Ser Ser Ala Ile Asp Ile Asp	
165 170 175 180	
GCT ACT GGC TTA GAT GCA GAA GAA AAT GAT ATT CCA GCA AAC CAC CGC	810
Ala Thr Gly Leu Asp Ala Glu Glu Asn Asp Ile Pro Ala Asn His Arg	
185 190 195	
TCC CCT AAA CCC AGT GCA AAC AGT GTA ACG TCA CCC CAC TCC AAA GAG	858
Ser Pro Lys Pro Ser Ala Asn Ser Val Thr Ser Pro His Ser Lys Glu	

200

205

210

BNSDOCID: <WO__9504822A1_I_>

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BNSDOCID: <WO___9504822A1_I_>

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GTGATGTTAG	TGTTTTAAGA	AATGTAGTTG	ATGTATCCAA	CAAGCCAGAA	TCAGCACAGA	2418
TAAAAAGTGG	AATTTCTTGT	TTCTCCAGAT	TTTAAATACG	TTAATACGCA	GGCATCTGAT	2478
TTGCATATTC	ATTCATGGAC	CACTGTTTCT	TGCTTGTACC	TCTGGCTGAC	TAAATTTGGG	2538
GACAGATTCA	GTCTTGCCTT	ACACAAAGGG	GATCATAAAG	TTAGAATCTA	TTTTCTATGT	2598
ACTAGTACTG	TGTACTGTAT	AGACAGTTTG	TAAATGTTAT	TTCTGCAAAC	AAACACCTCC	2658
TTATTATATA	TAATATATAT	ATATATATCA	GTTTGATCAC	ACTATTTTAG	AGTC	2712

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WHAT IS CLAIMED IS:

1. An isolated DNA fragment, comprising a sequence of nucleotides that encodes an α_1 subunit selected from the group consisting of α_{1A-1} , α_{1A-2} , α_{1E-1} , α_{1C-2} and α_{1E-3} .
- 5 2. The DNA fragment of claim 1, wherein the α_1 subunit is α_{1A-1} or α_{1A-2} .
3. The DNA fragment of claim 1, wherein the α_1 subunit is α_{1E-1} or α_{1E-3} .
4. The DNA fragment of claim 1, wherein the α_1 subunit
10 is α_{1C-2} .
5. An isolated DNA fragment, comprising a sequence of nucleotides that encodes a β subunit selected from the group consisting of β_2 , β_3 and β_4 .
6. The DNA fragment of claim 5, wherein the subunit is
15 a β_{2C} , β_{2D} or β_{2E} subunit.
7. The DNA fragment of claim 5, wherein the subunit is a β_3 subunit.
8. The DNA fragment of claim 7, wherein the subunit is a β_{3-1} subunit.
- 20 9. The DNA fragment of claim 5, wherein the subunit is a β_4 subunit.
10. The DNA fragment of claim 9, wherein the subunit has an amino acid sequence set forth in SEQ ID No. 28.
11. A eukaryotic cell, comprising heterologous DNA that
25 encodes an α_1 subunit selected from the group of subunits consisting of α_{1A-1} , α_{1A-2} , α_{1C-2} , α_{1E-1} , and α_{1E-3} .
12. A eukaryotic cell, comprising heterologous DNA that encodes an α_1 subunit and heterologous DNA that encodes a β subunit, wherein at least one subunit is selected from the
30 group of subunits consisting of α_{1A-1} , α_{1A-2} , α_{1C-2} , α_{1E-1} , α_{1E-3} , β_{2C} , β_{2D} , β_{2E} , β_{3-1} , a β_4 subunit.
13. The eukaryotic cell of claim 12, wherein the β subunit is a β_2 subunit.
14. The eukaryotic cell of claim 12, wherein the β
35 subunit is a β_4 subunit.

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15. The eukaryotic cell of claim 11, selected from the group consisting of HEK 293 cells, Chinese hamster ovary cells, African green monkey cells, and mouse L cells.

5 16. The eukaryotic cell of claim 12 selected from the group consisting of HEK 293 cells, Chinese hamster ovary cells, African green monkey cells, and mouse L cells.

17. A eukaryotic cell with a functional, heterologous calcium channel, produced by a process comprising:
10 introducing into the cell heterologous nucleic acid that encodes an α_1 -subunit of a human calcium channel, wherein:

the α_1 subunit is selected from the group consisting of α_{1A-1} , α_{1A-2} , α_{1C-2} , α_{1E-1} and α_{1E-3} ;

the heterologous calcium channel contains at least one subunit encoded by the heterologous nucleic acid; and

15 the only heterologous ion channels are calcium channels.

18. A eukaryotic cell with a functional, heterologous calcium channel, produced by a process comprising:

introducing into the cell nucleic acid that encodes an α_1 subunit of a human calcium channel and introducing into the
20 cell nucleic acid that encodes a β subunit of a human calcium channel, wherein:

at least one of the subunits is selected from the group consisting of α_{1A-1} , α_{1A-2} , α_{1E-1} , α_{1E-3} , β_{2C} , β_{2D} , β_{2E} , a β_3 , and a β_4 subunit;

25 the heterologous calcium channel contains at least one subunit encoded by the heterologous nucleic acid; and

the only heterologous ion channels are calcium channels.

19. The eukaryotic cell of claim 17 selected from the group consisting of HEK 293 cells, Chinese hamster ovary
30 cells, African green monkey cells, mouse L cells and amphibian oocytes.

20. The eukaryotic cell of claim 18 selected from the group consisting of HEK 293 cells, Chinese hamster ovary cells, African green monkey cells, mouse L cells and amphibian
35 oocytes.

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21. The eukaryotic cell of claim 18, wherein the β subunit is a β_2 , β_3 or β_4 subunit of a human calcium channel.

22. The eukaryotic cell of claim 18, wherein the calcium channel includes an α_{2b} subunit of a human calcium channel, an
5 α_{1B-1} subunit of a human calcium channel and a β_3 subunit of a human calcium channel.

23. The eukaryotic cell of claim 18, wherein the calcium channel includes an α_{1B-1} , α_{2b} , and a β_{1-2} subunit, or an α_{1B-1} , α_{2b} , and a β_{1-3} subunit, or an α_{1B-2} , α_{2b} , and a β_{1-3} subunit, or
10 an α_{1A-2} , α_{2b} , and a β_{3-1} subunit, or a α_{1B-1} , α_{2b} , and an β_{3-1} subunit.

24. The eukaryotic cell of claim 18, wherein the calcium channel contains an α_{2b} subunit of a human calcium channel, an α_{1B} or an α_{1D} subunit of a human calcium channel and
15 a β_{1-1} , β_{1-2} or β_{1-3} subunit of a human calcium channel.

25. A method for identifying a compound that modulates the activity of a calcium channel, comprising;

suspending a eukaryotic cell that has a functional, heterologous calcium channel, in a solution containing the
20 compound and a calcium channel-selective ion:

depolarizing the cell membrane of the cell; and

detecting the current flowing into the cell,

wherein:

the heterologous calcium channel includes at least one
25 human calcium channel subunit encoded by DNA or RNA that is heterologous to the cell;

at least one subunit is selected from the group consisting of α_{1A-1} , α_{1A-2} , α_{1E-1} , α_{1E-3} , α_{1C-2} , β_{2C} , β_{2D} , β_{2E} , a β_3 subunit and a β_4 subunit;

30 the current that is detected is different from that produced by depolarizing the same or a substantially identical cell in the presence of the same calcium channel selective ion but in the absence of the compound.

26. The method of claim 25, wherein the heterologous DNA
35 or RNA encodes a β_3 subunit.

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27. The method of claim 26, wherein the heterologous DNA or RNA encodes a β_4 subunit.

28. A subunit-specific antibody selected from the group consisting of antibodies that bind to an α subunit type or α subunit subtype of a human calcium channels, wherein the subunit is an α_1 subunit.

29. The antibody of claim 28, wherein antibody is subtype specific and the α_1 subunit is α_{1A} , α_{1E} and α_{1B} .

30. An RNA or single-stranded DNA probe of at least 16 bases in length comprising at least 16 substantially contiguous bases from nucleic acids that encode a subunit of a human calcium channel selected from the group of subunits consisting of α_{1A-1} , α_{1A-2} , α_{1E-1} , α_{1C-2} , α_{1E-3} , β_{3-1} , β_{2C} , β_{2D} , β_{2E} and β_4 .

31. The probe of claim 30 that contains at least 30 bases that are from nucleic acids that encode a subunit of a human calcium channel selected from the group of subunits consisting of α_{1A-1} , α_{1A-2} , α_{1E-1} , α_{1C-2} , α_{1E-3} , β_{3-1} , β_{2C} , β_{2D} , β_{2E} and β_4 subunits.

32. A method for identifying nucleic acids that encode a human calcium channel subunit, comprising hybridizing under conditions of at least low stringency a probe of claim 30 to a library of nucleic acid fragments, and selecting hybridizing fragments.

33. A method for identifying cells or tissues that express a calcium channel subunit-encoding nucleic acid, comprising hybridizing under conditions of at least low stringency a probe of claim 30 with mRNA expressed in the cells or tissues or cDNA produced from the mRNA, and thereby identifying cells or tissue that express mRNA that encodes the subunit.

34. A substantially pure human calcium channel subunit selected from the group consisting of α_{1A-1} , α_{1A-2} , α_{1E-1} , α_{1C-2} , α_{1E-3} , β_{3-1} , β_{2C} , β_{2D} , β_{2E} and β_4 .

INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/US 94/09230

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C12N5/10 G01N33/50 C07K16/28 C12Q1/68
C07K14/705

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 04083 (THE SALK INSTITUTE BIOTECHNOLOGY/INDUSTRIAL ASSOCIATES, INC.) 4 March 1993 see page 8, line 12 - page 10, line 33 see page 11, line 10 - page 12, line 9 see page 12, line 15 - page 13, line 18 see page 23, line 13 - page 26, line 3 see page 29, line 31 - page 30, line 3 see page 31, line 28 - page 32, line 15 see page 33, line 13 - line 30 see page 35, line 4 - line 32 see page 37, line 3 - line 16 see page 28, line 25 - page 44, line 34 see page 59, line 11 - line 23 see SEQ ID NO. 3 see SEQ ID NO. 10 --- -/--	1,4,5,7, 11,17, 25,26, 28-32,34

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

7 December 1994

Date of mailing of the international search report

21.12.94

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INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/US 94/09230

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>NEURON, vol.8, no.1, January 1992 pages 71 - 84 MARK E. WILLIAMS ET AL. 'Structure and functional expression of alpha1, alpha2, and beta subunits of a novel human neuronal Calcium channel subtype' see summary see page 71, right column, paragraph 3 - page 74, right column, paragraph 3 see page 80, right column, paragraph 2 see page 82, left column, last paragraph - right column, paragraph 1 ----</p>	5,7
X	<p>EMBO JOURNAL, vol.11, no.3, March 1992, EYNHAM, OXFORD GB pages 885 - 890 ROGER HULLIN ET AL. 'Calcium channel beta subunit heterogeneity: functional expression of cloned cDNA from heart, aorta and brain' see abstract see page 885, right column, paragraph 2 ----</p>	5,7
A	<p>JOURNAL OF CELLULAR BIOCHEMISTRY. KEYSTONE SYMPOSIA ON MOLECULAR & CELLULAR BIOCHEMISTRY. April 1992, 16E, page 224 P. BRUST ET AL.: 'Expression of human neuronal voltage-dependent Calcium channel in transfected HEK293 cells.' see abstract T100 ----</p>	1,5,11, 12, 15-22, 25,34
P,O, X	<p>SOCIETY FOR NEUROSCIENCE ABSTRACTS. 23RD ANNUAL MEETING OF THE SOCIETY OF NEUROSCIENCE, WASHINGTON 1993, vol.19, no.1-3, November 1993 page 11 L. MARUBIO ET AL. 'Cloning and functional expression of human alpha1E high-voltage activated Calcium channel' see abstract no. 11.5 ----</p>	1,3,11, 12,15, 17,19,34
P,X	<p>EUROPEAN JOURNAL OF BIOCHEMISTRY, vol.220, no.1, February 1994 pages 257 - 262 THIBAUT COLLIN ET AL. 'Cloning, chromosomal location and functional expression of the human voltage-dependent calcium-channel beta3 subunit' see abstract see page 258, left column, last paragraph - right column, paragraph 1 -----</p>	5,7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 94/09230

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9304083	04-03-93	AU-A ^u 2495792	16-03-93
		CA-A- 2113203	04-03-93
		EP-A- 0598840	01-06-94
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